Arena

Lorcaserin for Weight Management

As an adjunct to diet and exercise for weight management, including weight loss and maintenance of weight loss

Lorcaserin for Weight Management

Craig Audet
Vice President, Global Regulatory Affairs
Arena Pharmaceuticals

Arena and Eisai Partnership

- Arena is the developer of lorcaserin
- Eisai will market and distribute lorcaserin in the United States

Lorcaserin Proposed Indication

- As an adjunct to diet and exercise for weight management, including weight loss and maintenance of weight loss
  - Obese patients (BMI ≥ 30 kg/m^2)
  - Overweight patients (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbid condition
    - hypertension
    - dyslipidemia
    - cardiovascular disease
    - glucose intolerance
    - sleep apnea
    - type 2 diabetes

Overview: Lorcaserin Phase 3 Results

- Study 009 and 011 (Patients without diabetes)
  - ≥ 5% weight loss
    - Lorcaserin ~47% vs. Placebo ~23%
  - ≥ 10% weight loss
    - Lorcaserin ~22% vs. Placebo ~9%
- Study 010 (Patients with type 2 diabetes)
  - ≥ 5% weight loss
    - Lorcaserin 38% vs. Placebo 16%
  - ≥ 10% weight loss
    - Lorcaserin 16% vs. Placebo 4%

Lorcaserin Benefit / Risk

- Study 010 further enhances the benefit profile established in Study 009 & 011
  - Significant weight loss
  - Efficacy met FDA defined benchmark
  - Improvement in CV risk biomarkers
  - Clinically meaningful reductions in HbA1c and fasting plasma glucose

Overview: Lorcaserin Preclinical Data

- Re-adjudicated female mammary 2-year findings
- 70-fold safety margin for astrocytoma
- 24-fold safety margin for mammary adenocarcinoma
- Prolactin mechanism for fibroadenoma
- New data mitigate clinical risk

Sponsor Presentation Outline

Clinical Study Designs and Patient Baseline Characteristics	**William Shanahan, MD** Sr. VP & CMO Arena Pharmaceuticals
Efficacy Results and Clinical Perspective	**Steven R. Smith, MD** Scientific Director, Translational Research Institute for Metabolism and Diabetes, Florida Hospital / Sanford Burnham Institute
Clinical Safety Results	**William Shanahan, MD** Sr. VP & CMO Arena Pharmaceuticals
Preclinical Studies	**Dominic Behan, PhD** Exec. VP & CSO Arena Pharmaceuticals
Preclinical Safety Relevance to Human Risk	**Samuel Cohen, MD, PhD** Professor of Pathology/Microbiology and Endowed Professor of Oncology, UNMC Fellow, Academy of Toxicological Sciences
Concluding Remarks	**Dominic Behan, PhD** Exec. VP & CSO Arena Pharmaceuticals

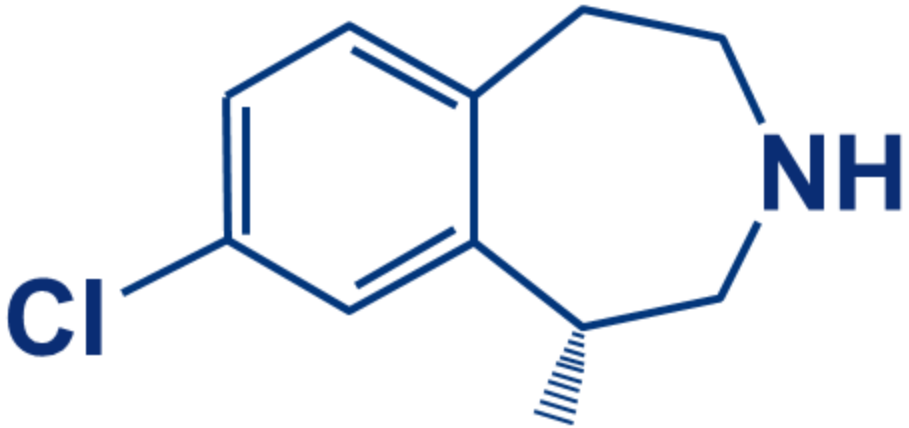
Sponsor Outside Experts

Gary Koch, PhD	Professor, Biostatistics, University of North Carolina at Chapel Hill
Jose Russo, MD, FACP	Professor, Fox Chase Cancer Center; Director, NCI-NIEHS Breast Cancer & Environmental Research Center
Ken Schafer, DVM, PhD, DACVP	Senior Pathologist, Vet Path Services
Benjamin Scirica, MD, MPH, FACC	Cardiovascular Division, Brigham and Women's Hospital; Asst. Professor of Medicine, Harvard Medical School; Investigator, The TIMI Study Group
Neil Weissman, MD	President, MedStar Health Research Institute Professor of Medicine, Georgetown University
Gary Williams, MD	Professor of Pathology, Professor of Clinical Public Health, New York Medical College

Phase 3 Clinical Study Designs and Patient Baseline Characteristics

William Shanahan, MD
Sr. Vice President & Chief Medical Officer
Arena Pharmaceuticals

Lorcaserin is a Selective Serotonin 2C Receptor Agonist



Human	5-HT_{2C}R	5-HT_{2A}R	5-HT_{2B}R
Functional Activity EC_{50} (nM)	39	553	2,380
Relative Selectivity		14	61

Phase 3, Double Blind, Randomized Controlled Trials

	Study 009	Study 011	Study 010
Overview	Non-diabetic patients 18-65 yrs old		Type 2 diabetes 18-65 yrs old
BMI Range	27 to 45	27 to 45	27 to 45
N	3,182	4,008	604
Lorcaserin BID Lorcaserin QD	1,595 0	1,603 802	256 95
Length of study	2 years	1 year	1 year
Lifestyle Modification	All patients followed a daily 600 calorie deficit diet + exercise program, with monthly counseling sessions		

Person Years of Exposure in Phase 3 Studies 009, 010 and 011

Treatment Group	Total # of Subjects on Study Drug	Duration of Treatment		
		Exposure Person-Years	Range Days Min-Max	Mean (SD) Days
10 MG BID	3,451	2,949	1-779	316.0 (207.85)
10 MG QD	896	670	1-400	277.1 (129.16)
Any Dose	4,347	3,618	1-779	308.0 (194.90)

As Treated

Pivotal Study Design: Primary Efficacy Endpoints

- Year 1 (ordered primary endpoints)
  - Proportions achieving ≥ 5% weight loss
  - Absolute weight loss
  - Proportions achieving ≥ 10% weight loss

Baseline Demographics

Parameter	Study 009		Study 011		Study 010	
	PBO n=1,587	LOR n=1,595	PBO n=1,601	LOR n=1,602	PBO n=252	LOR n=256
Mean age (yrs)	44	44	44	44	52	53
Female	84%	83%	78%	81%	54%	54%
Mean weight (kg)	100	100	100	100	103	104
Mean BMI (kg/m^2)	36	36	36	36	36	36
Ethnicity						
Caucasian	66%	68%	67%	67%	66%	59%
African American	19%	19%	20%	19%	18%	22%
Hispanic/Latino	13%	11%	11%	11%	11%	15%
Other	2%	2%	2%	3%	6%	5%

Significant Medical Conditions or Impaired Fasting Glucose in Study 009 and 011

Parameter	Population Prevalence BMI ≥ 30 Male	Population Prevalence BMI ≥ 30 Female	Study 009	Study 011
Hypertension	38%	32% [a]	21%	24%
Dyslipidemia	20%	25% *[a]	33%	28%
Sleep apnea	> 15%[b]	> 15%[b]	4%	4%
CVD	> 8%	> 6%[c]	5%	5%
Impaired fasting glucose	32.6%	20%[a,d]	26%	25%
Depression	2.9%	6.7%[a]	8%	8%
No comorbid condition			50%	53%
≥ 1 comorbid condition			50%	47%
≥ 2 comorbid condition			16%	17%

* High cholesterol

[a] NHANES III; [b]Wisconsin Sleep Study; [c]AHA Heart Disease and Stroke Statistics; [d]All BMIs

Baseline Characteristics Study 010

	Study 010	
	PBO n=252	Lorcaserin 10 mg BID n=256
HbA1c		
Mean	8%	8%
≥ 9	18%	18%
< 9	82%	82%
Fasting plasma glucose (mg/dL)	160.2	163.8
Primary diabetic medications		
Metformin	91%	92%
SFU	50%	50%
Both	41%	43%
Duration of diabetes (years)	7.0	6.6

Patient Disposition

	Study 009		Study 011		Study 010	
	PBO n=1,587	LOR n=1,595	PBO n=1,601	LOR n=1,602	PBO n=252	LOR n=256
Completed	45%	55%	52%	57%	62%	66%
Completed and Returning Dropouts	57%	65%	59%	64%	65%	68%
Withdrawals:						
Lost to follow up	14%	12%	15%	12%	6%	8%
Adverse events	7%	7%	5%	7%	4%	9%
Lack of efficacy	6%	2%	4%	2%	2%	1%
Other	28%	24%	25%	21%	26%	17%

* Other includes the following withdrawal categories: Withdrawal of Consent, Lost to Follow-up, Protocol Deviation/Non-compliance, Sponsor Decision, PI Decision and Other

Efficacy Results and Clinical Perspective

Steven R. Smith, MD
Scientific Director
Translational Research Institute for Metabolism and Diabetes
Florida Hospital / Sanford Burnham Institute

Many Different Ways to Analyze the Data

- MITT with LOCF imputation
  - Patients receiving ≥ 1 dose
  - ≥ 1 post-baseline weight measurement
- ITT
  - LOCF imputation
  - BOCF imputation
- Completers
  - Those who stayed in the study
- Week 52 Population
  - Completers + dropouts returning for a Week 52 visit
- Responder Analyses

FDA Guidance for Primary Endpoints of Weight Loss Drugs

- ≥ 5% difference in mean weight loss between groups at one year

OR

- At least 35% of patients lose ≥ 5% body weight at one year and approximately double the proportion in the placebo-treated group

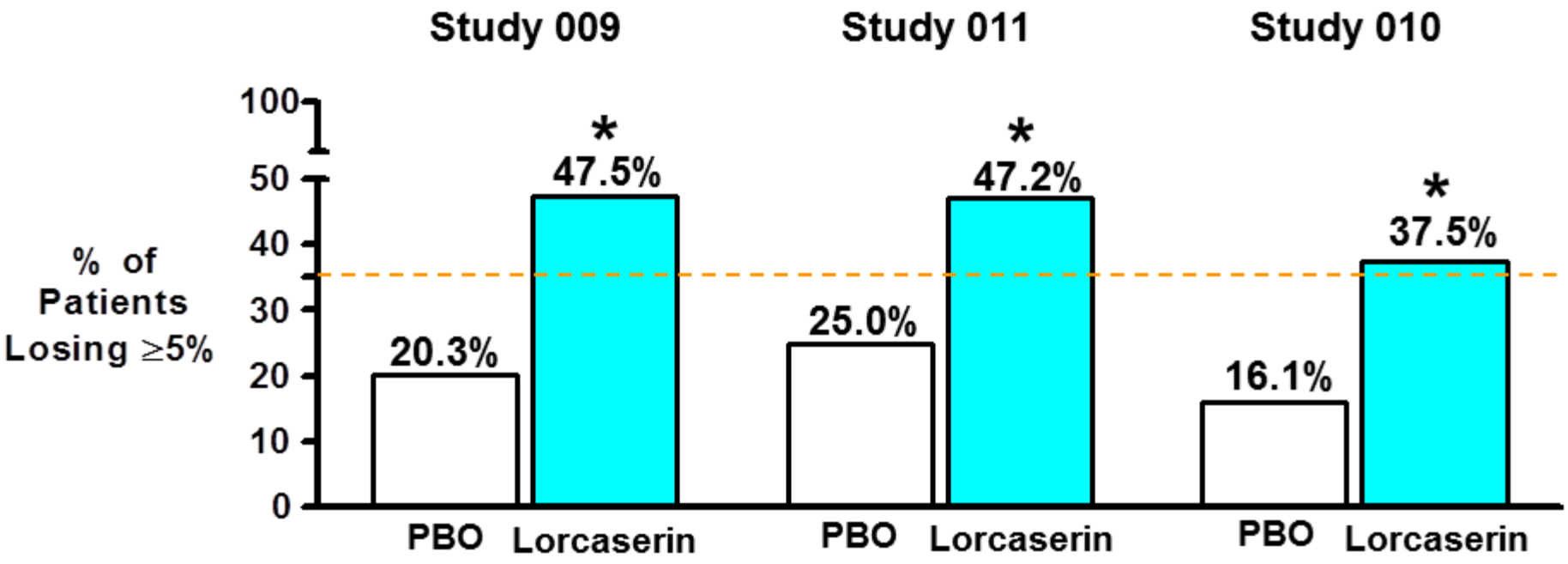
* Adapted from FDA Guidance for Industry Developing Products for Weight Management, February 2007

5% Weight Loss is Correlated with Improvements in Risk Factors

- Generally quoted as 5% based on
  - Improvements in cardiovascular risk factors
  - Improvements in glycemic control
  - Diabetes prevention

Douketis and Macie, et al. *Nature* 2005; Foreyt, et al Lifestyle Obesity Management, 2003 NHLBI website; Abel, et al. *Physiol Rev* 2008; Krauss, et al. *AHA Conference Proceedings: Obesity- Impact on Cardiovascular Disease* 1998; Wilson, et al. *Arch Intern Med* 2002

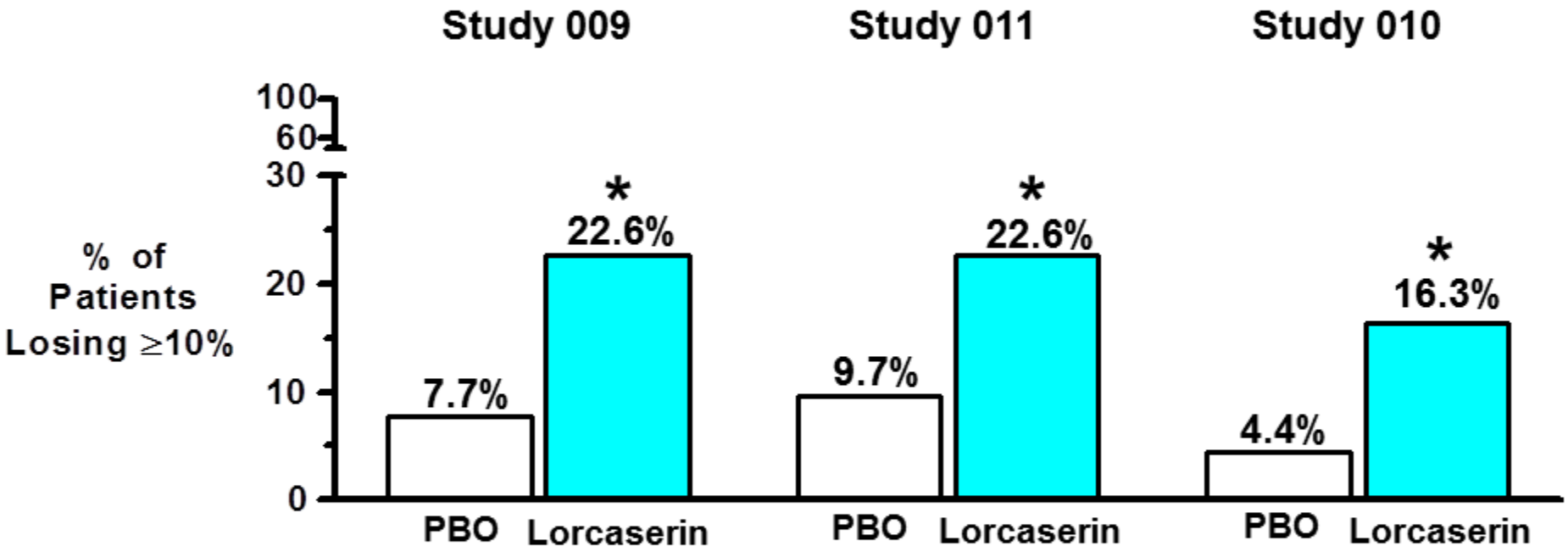
Proportion of Patients Losing ≥ 5% of Baseline Body Weight



	Study 009	Study 011	Study 010
Difference in Proportion vs. PBO	27.2%	22.2%	21.3%
95% CI	24.0%, 30.5%	18.9%, 25.5%	13.8%, 28.9%

* p-value < 0.001 vs. PBO
MITT Population

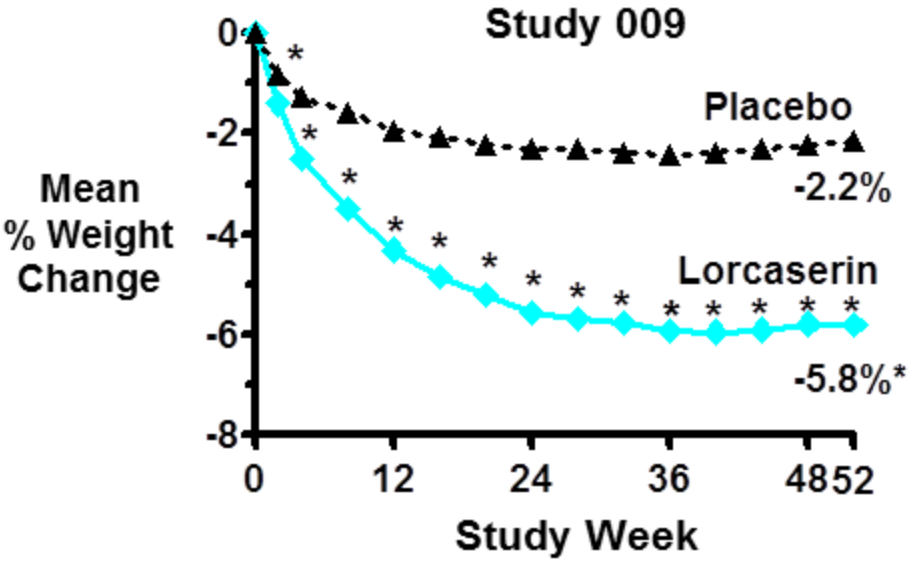
Proportion of Patients Losing ≥ 10% of Baseline Body Weight

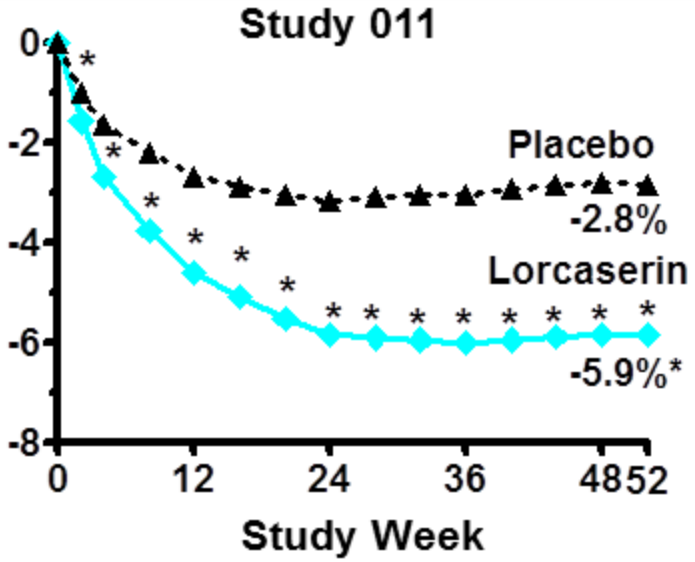


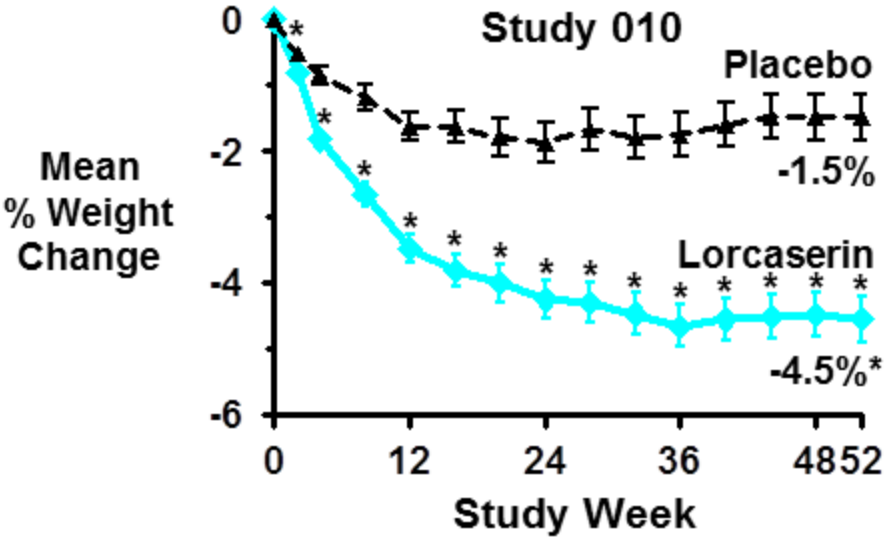
	Study 009	Study 011	Study 010
Difference in Proportion vs. PBO	14.9%	12.9%	11.9%
95% CI	12.4%, 17.4%	10.3%, 15.4%	6.7%, 17.1%

* p-value < 0.001 vs. PBO
MITT Population

Difference in Mean Weight Loss was Statistically Significant

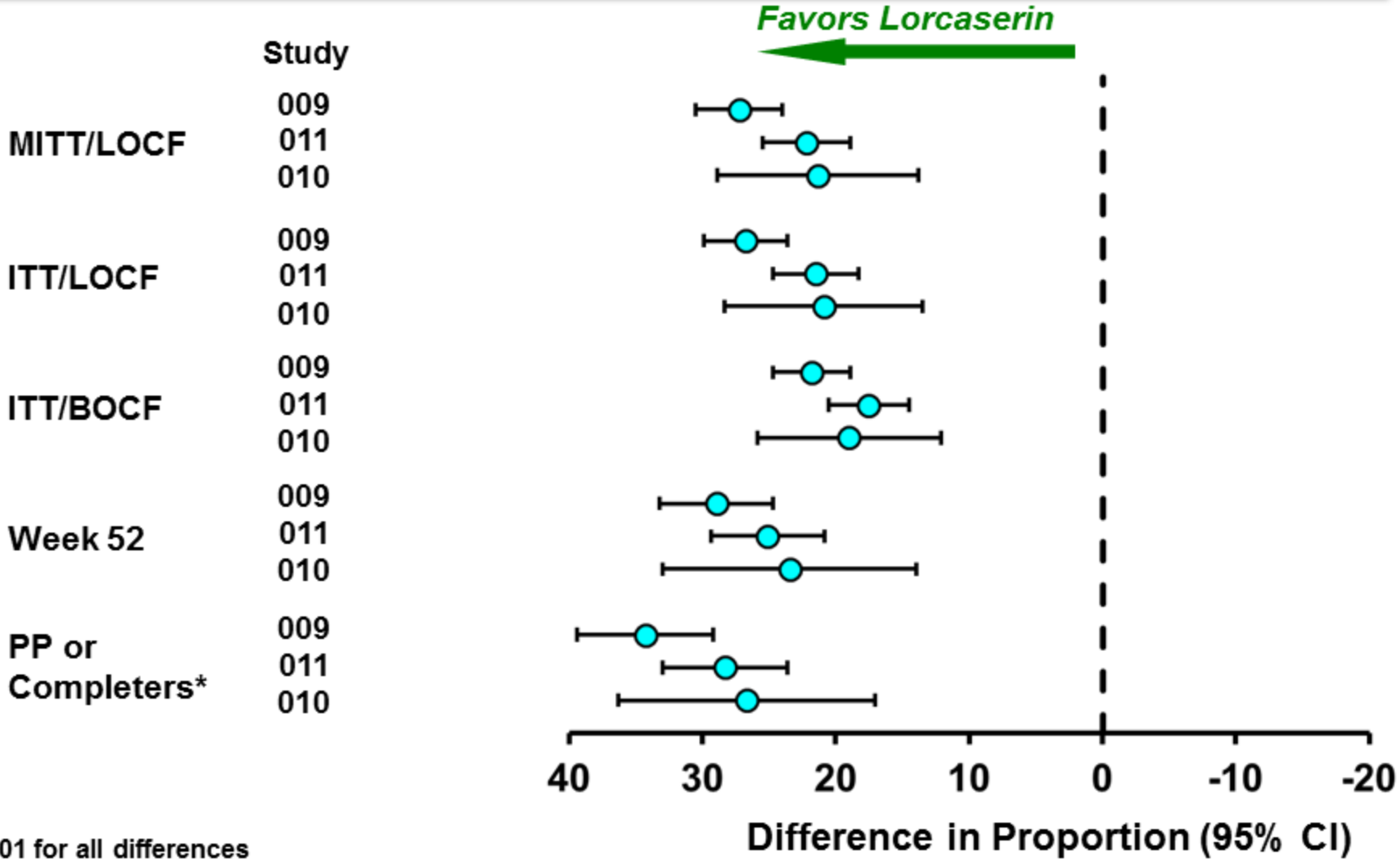






* p-value < 0.001 vs. PBO
MITT Population

Placebo-Adjusted Proportion of Patients who Lost ≥ 5% of Baseline Body Weight at Week 52



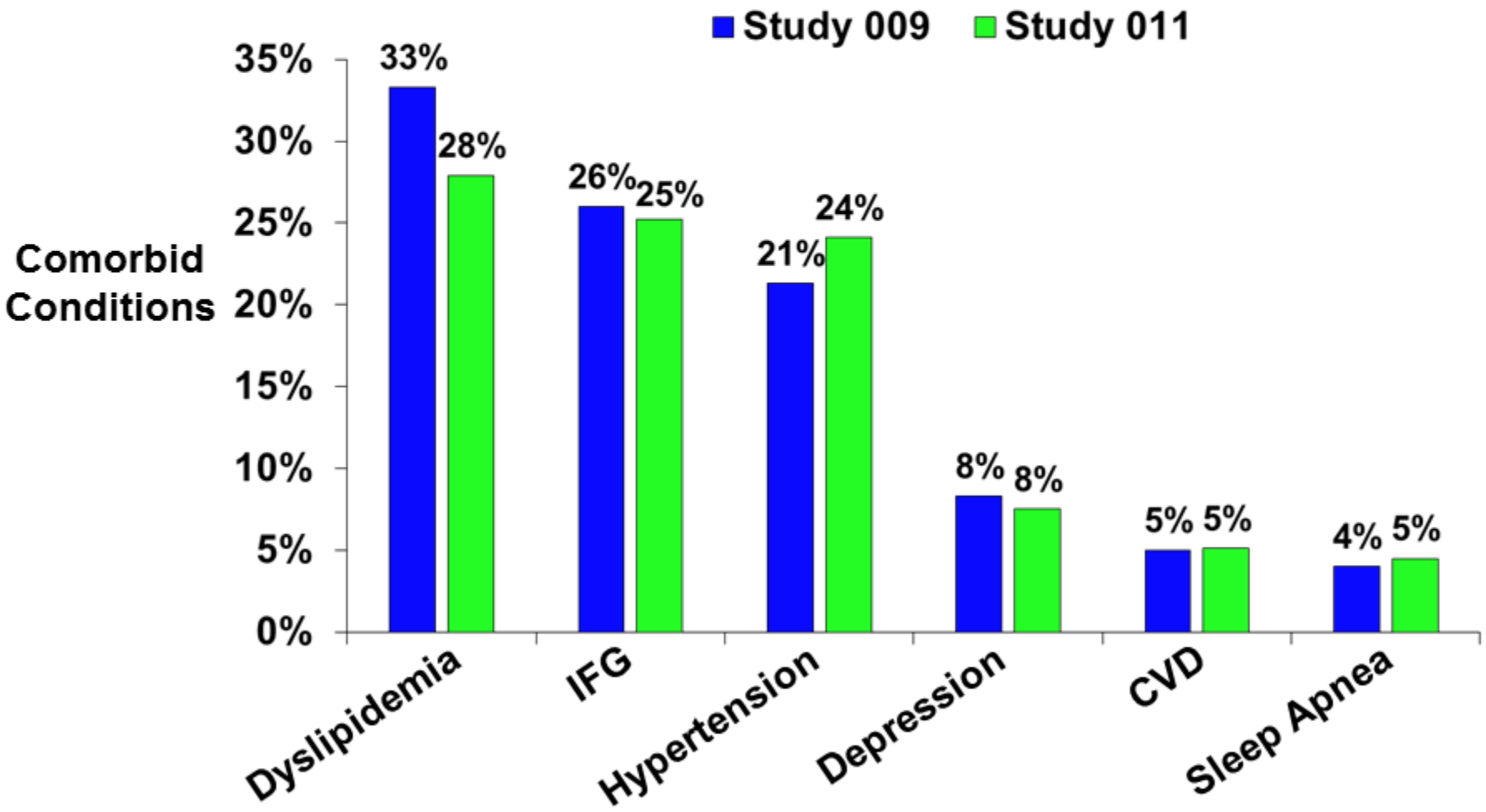
p < 0.001 for all differences

* Per protocol for Studies 009 and 011; completers for Study 010

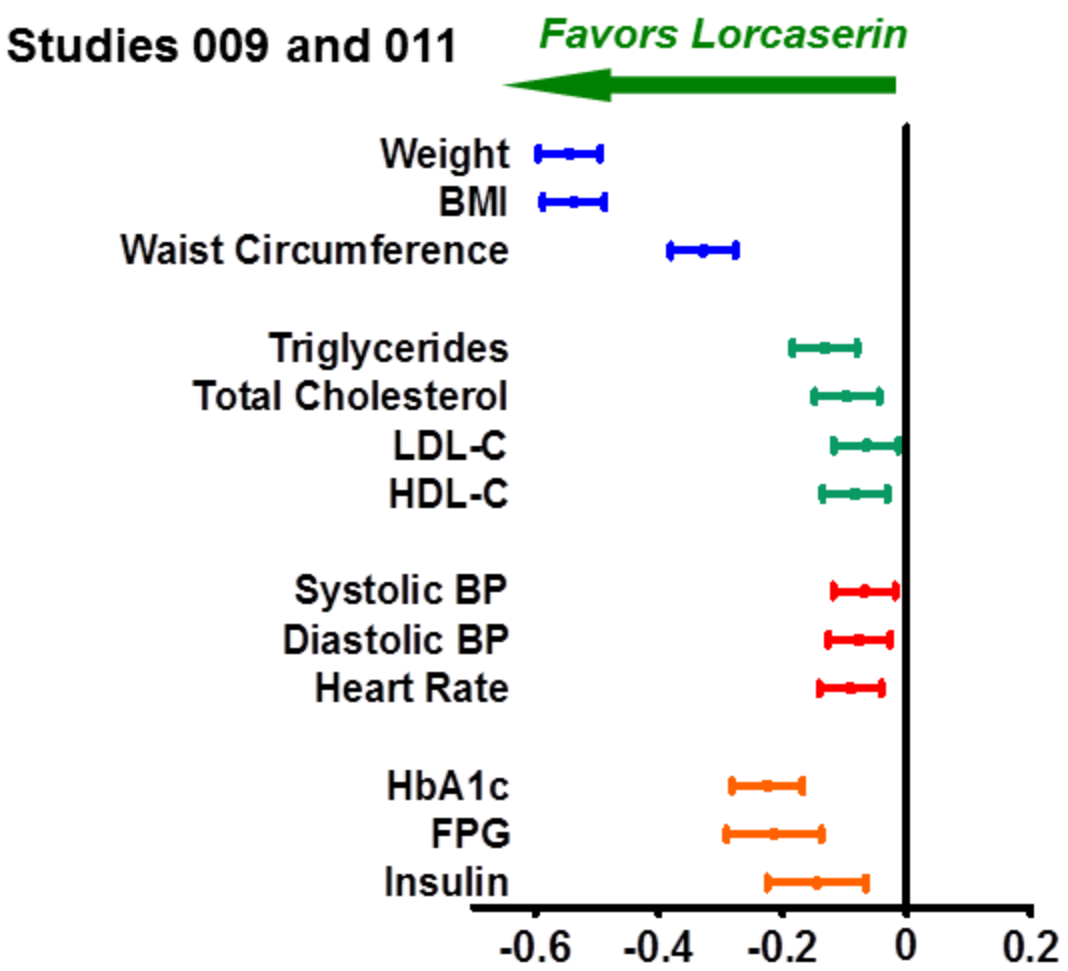
FDA Guidance for Secondary Endpoints of Weight Loss Drugs

- Improvements in markers of cardiovascular risk factors and changes in common weight-related comorbidities

Significant Medical Conditions or Impaired Fasting Glucose



Lorcaserin Showed Favorable Impact on Cardiometabolic Parameters



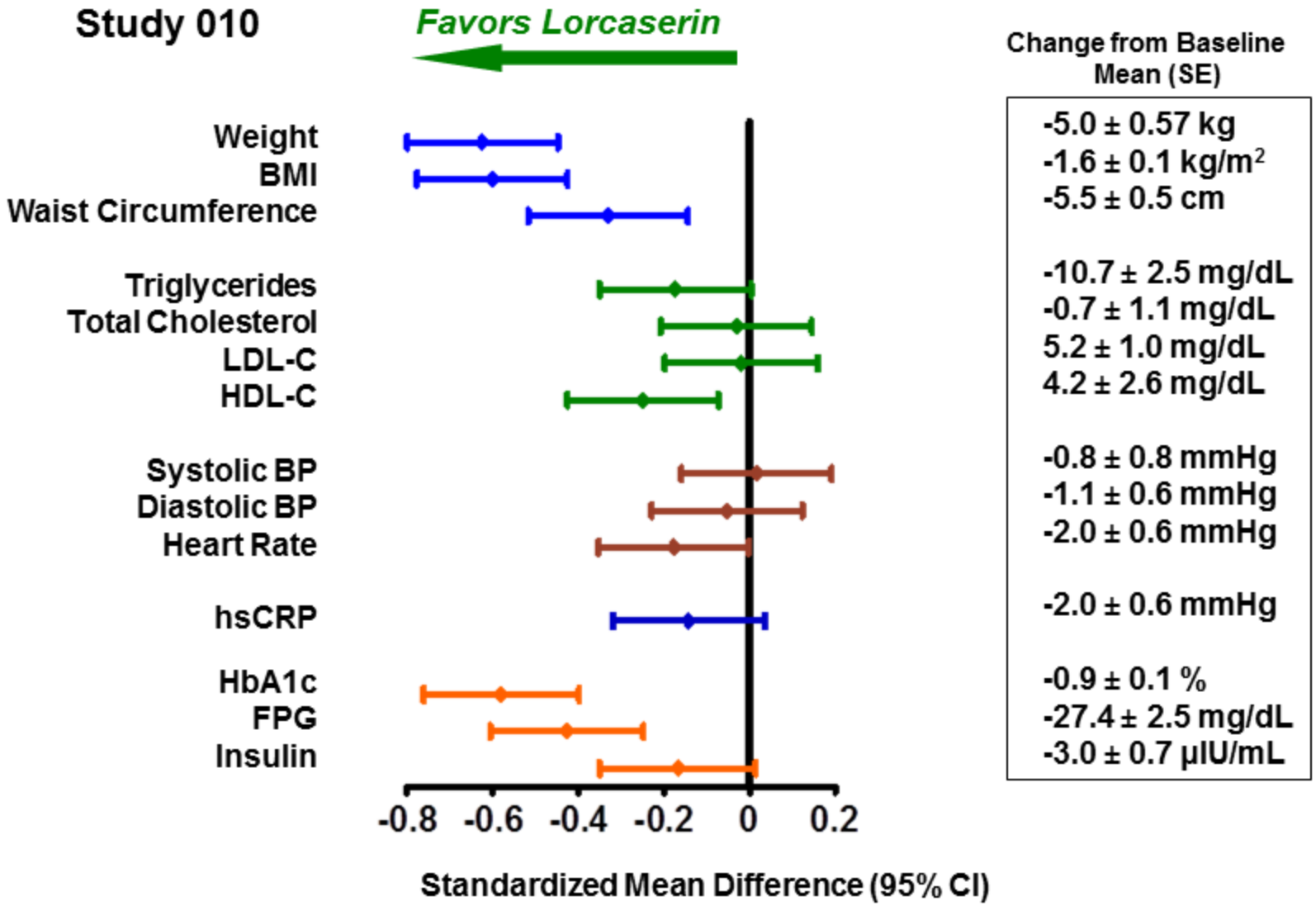
Change from Baseline Mean (SE)
-5.8 ± 0.12 kg
-2.1 ± 0.04 kg/m^2
-6.5 ± 0.15 cm
-5.2 ± 0.73 mg/dL
-0.8 ± 0.25 mg/dL
1.6 ± 0.40 mg/dL
1.8 ± 0.27 mg/dL
-1.7 ± 0.22 mmHg
-1.5 ± 0.16 mmHg
-1.2 ± 0.16 mmHg
-0.1 ± 0.01 %
-0.2 ± 0.19 mg/dL
-0.1 ± 0.01 µIU/mL

Blood Pressure and Heart Rate Change from Baseline at Week 52 Studies 009 and 011

Parameter / Treatment	n at Wk 52	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline LS Mean
Systolic BP (mm Hg)				
Placebo	3,039	121.0 (11.7)	120.2 (12.5)	-1.0 (0.2)
Lorcaserin 10 mg BID	3,096	121.4 (11.9)	119.7 (12.7)	-1.8 (0.2)
Diastolic BP (mm Hg)				
Placebo	3,039	77.7 (8.1)	76.7 (8.8)	-1.0 (0.2)
Lorcaserin 10 mg BID	3,096	77.4 (8.0)	75.9 (8.7)	-1.6 (0.2)
Heart Rate (bpm)				
Placebo	1,557	69.3 (8.7)	67.8 (9.3)	-1.5 (0.2)
Lorcaserin 10 mg BID	1,798	69.0 (8.8)	66.9 (9.1)	-2.2 (0.2)

Population: MITT/LOCF; Except for Heart Rate where Safety Population was used (SEM)

Lorcaserin Showed Favorable Impact on Cardiometabolic Parameters



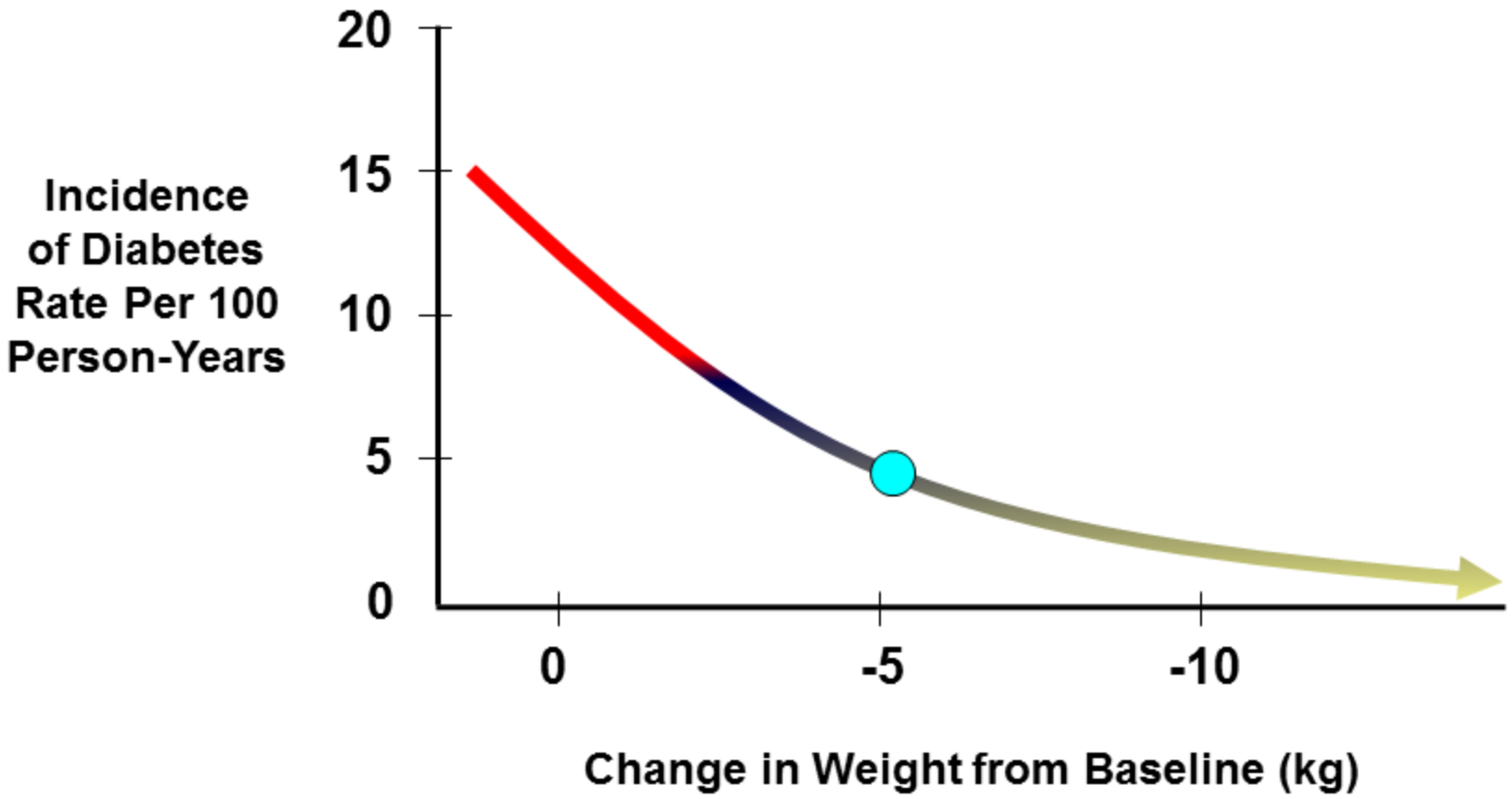
Summary of CV Vital Signs and Change from Baseline in Study 010

Parameter / Treatment	n at Wk 52	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline LS Mean
Systolic BP (mm Hg)				
Placebo	248	126.5 (13.5)	125.6 (13.5)	-0.9 (0.9)
Lorcaserin 10 mg BID	251	126.6 (12.7)	125.8 (12.5)	-0.8 (0.9)
Diastolic BP (mm Hg)				
Placebo	248	78.7 (7.9)	77.5 (8.2)	-0.7 (0.6)
Lorcaserin 10 mg BID	251	77.9 (8.0)	76.8 (8.9)	-1.1 (0.6)
Heart Rate				
Placebo	158	72.4 (9.4)	72.5 (10.2)	0.1 (0.7)
Lorcaserin 10 mg BID	170	72.8 (9.7)	70.7 (9.3)	-2.1 (0.8)

Population: MITT/LOCF; Except for Heart Rate where Safety Population was used (SEM)

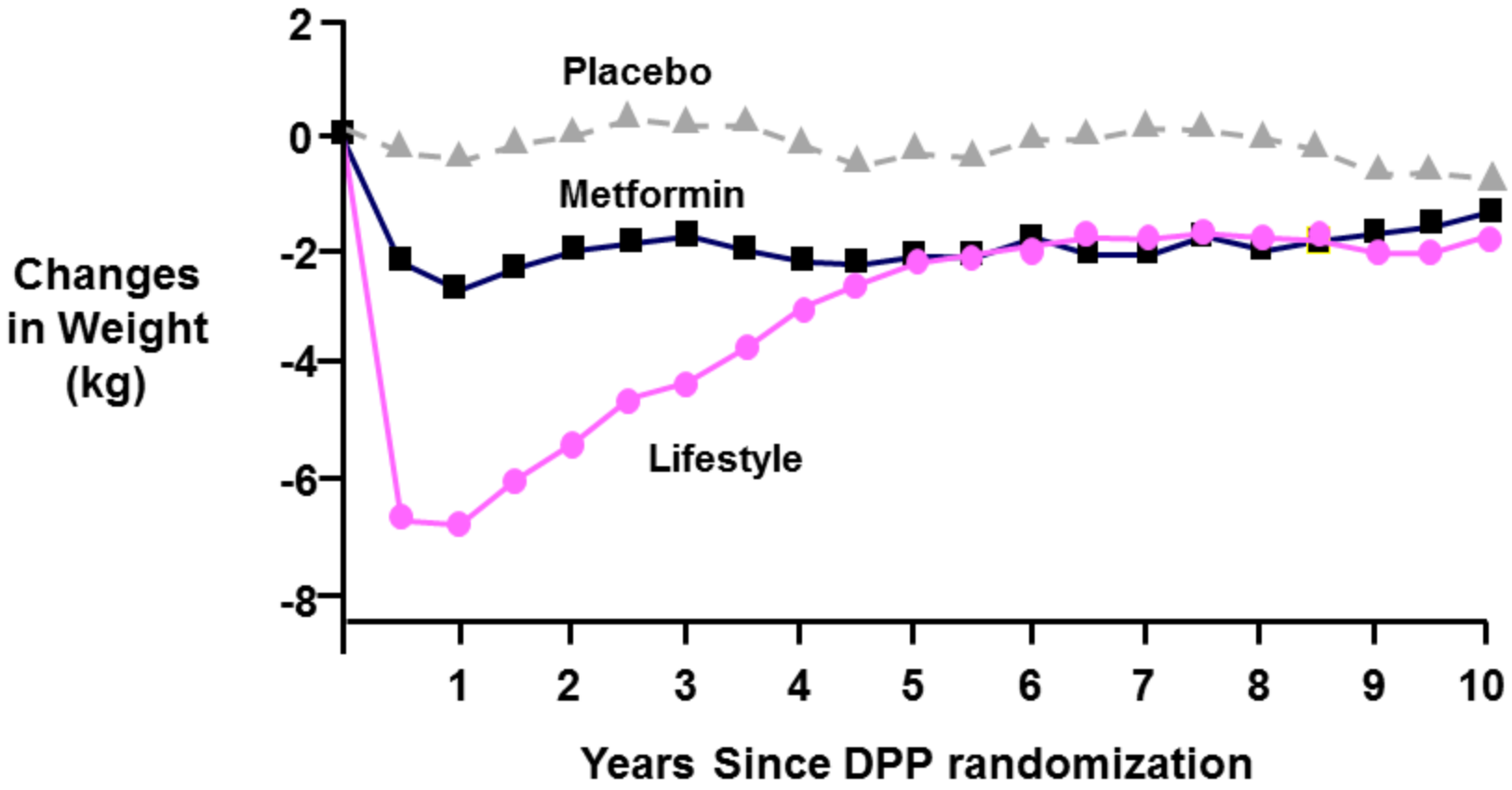
Weight Loss and the Prevention of Diabetes

5% Weight Loss in Context to the Diabetes Prevention Program (DPP)



Adapted from: Hamman, et al. *Diabetes Care* 29:2102-2107, 2006

Diabetes Prevention Program (DPP) 10-Year Results



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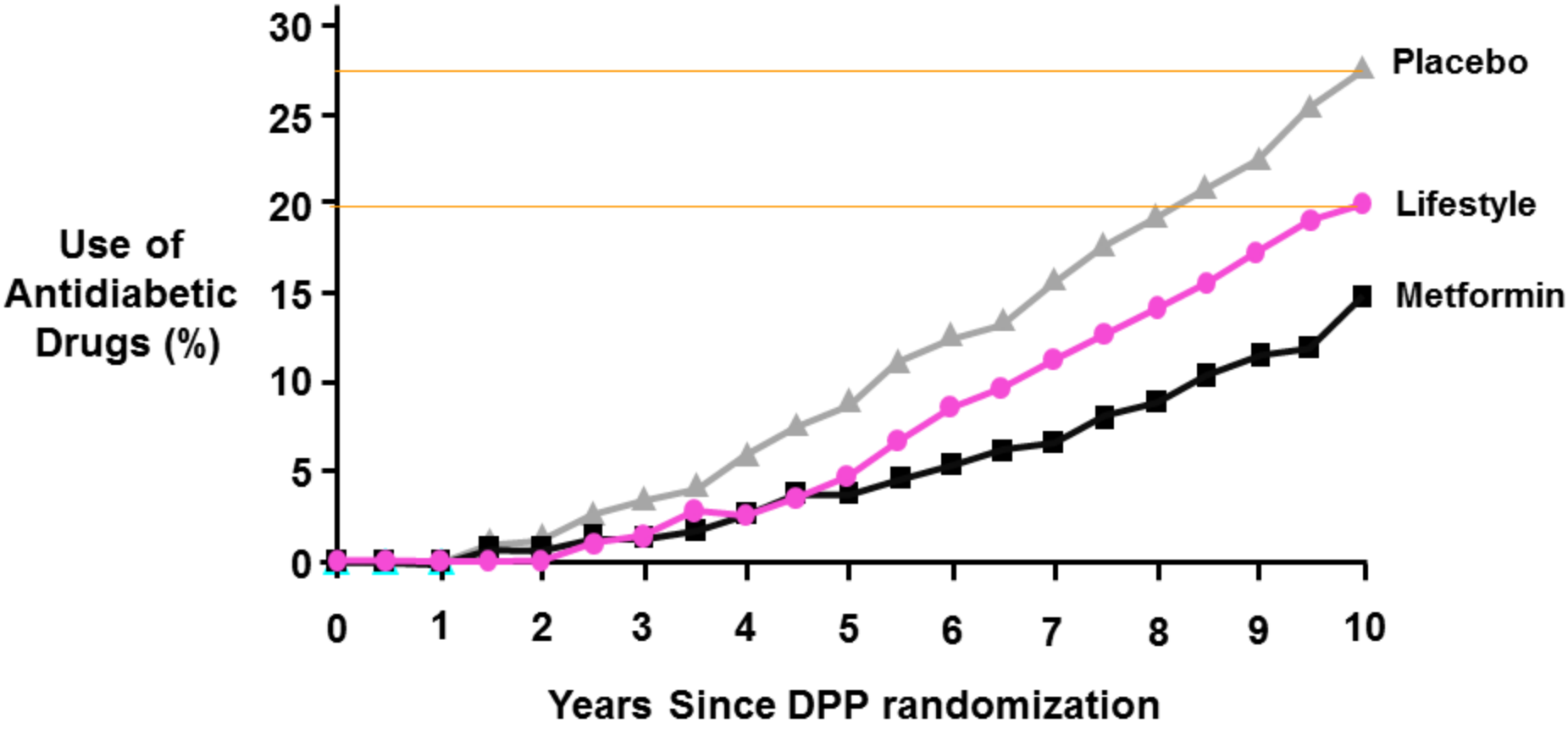
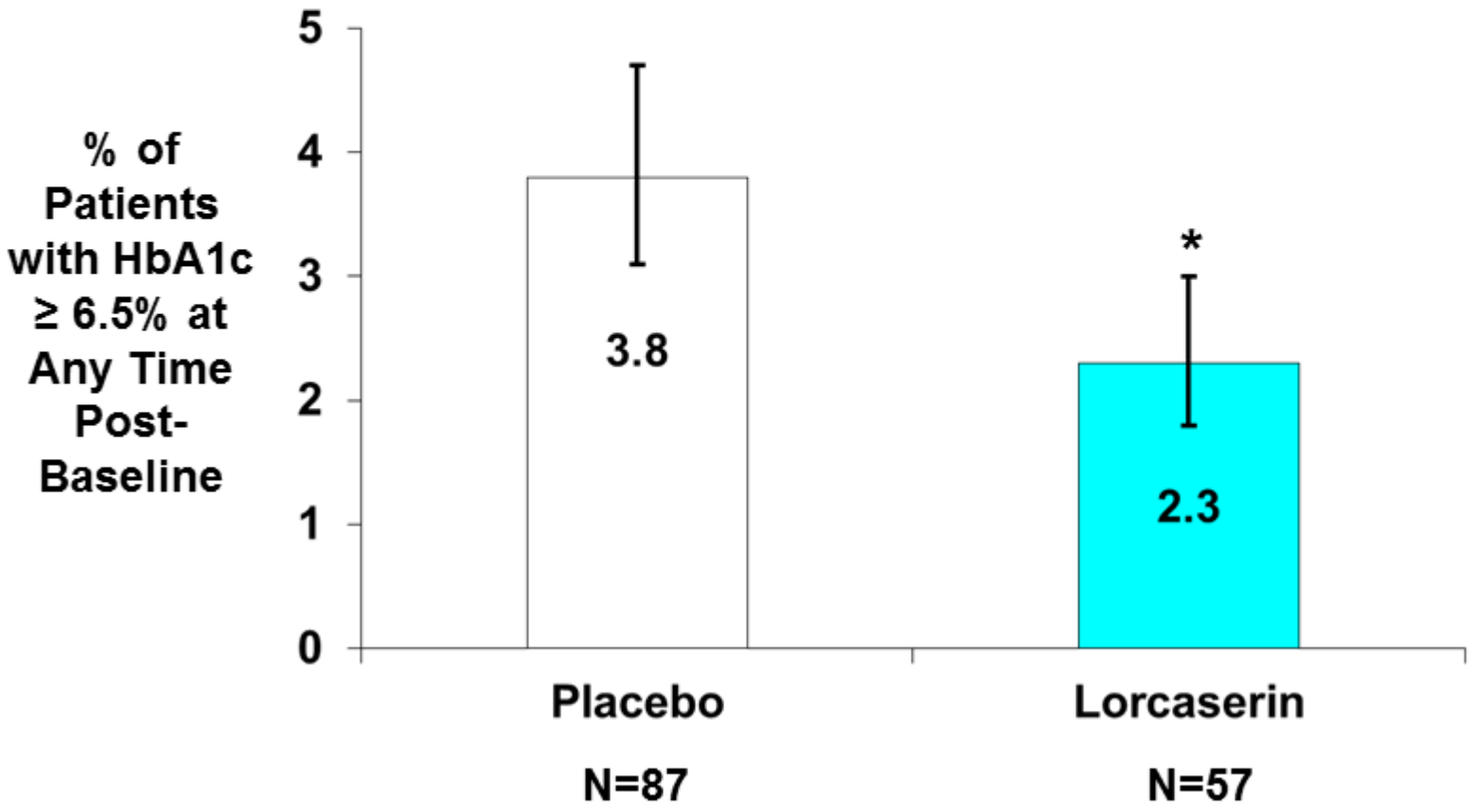
Diabetes Prevention Program (DPP) 10-Year Results



Lancet Vol 374 November 14, 2009

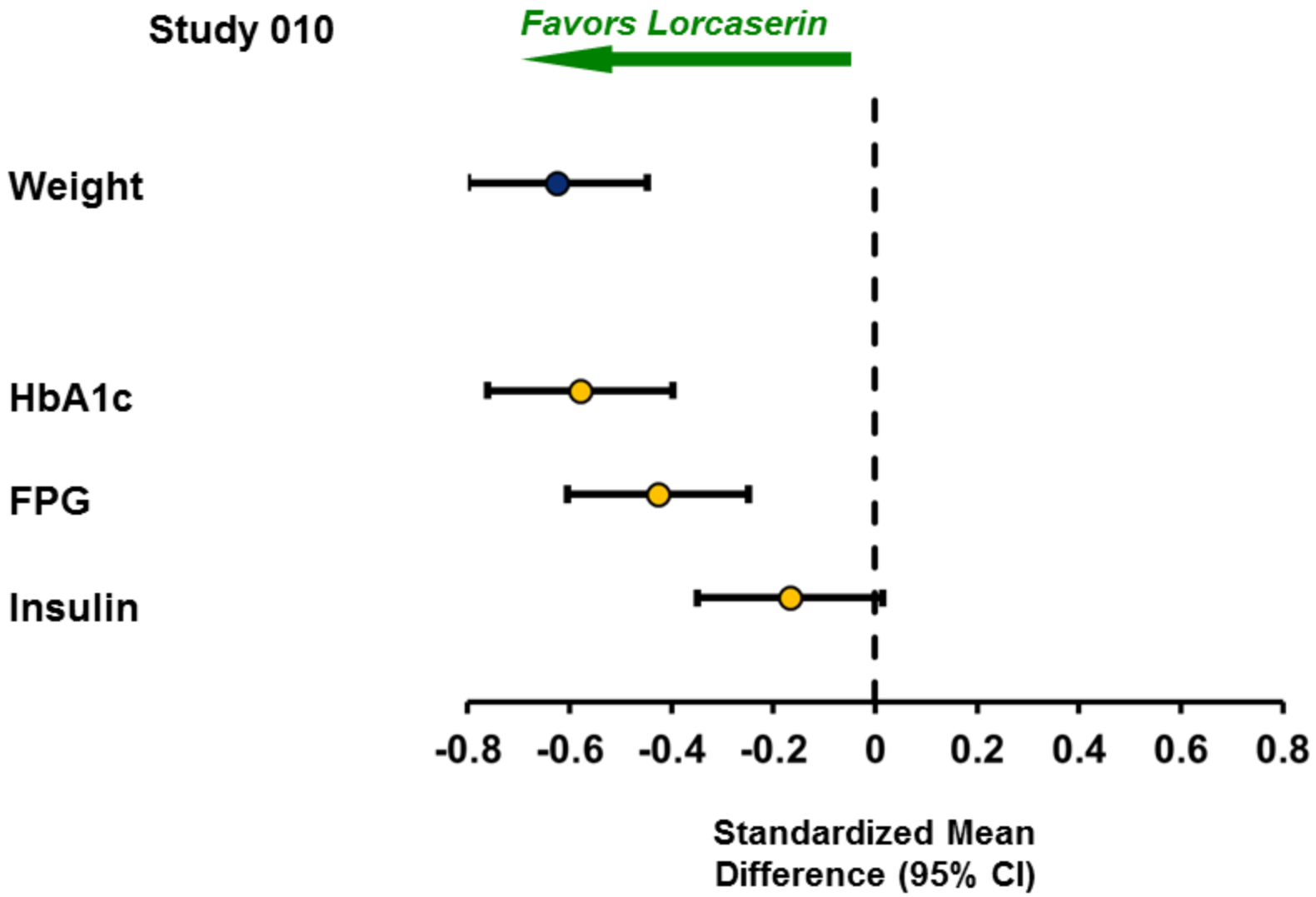
New Onset Type 2 Diabetes in Patients Without Diabetes in Studies 009 & 011



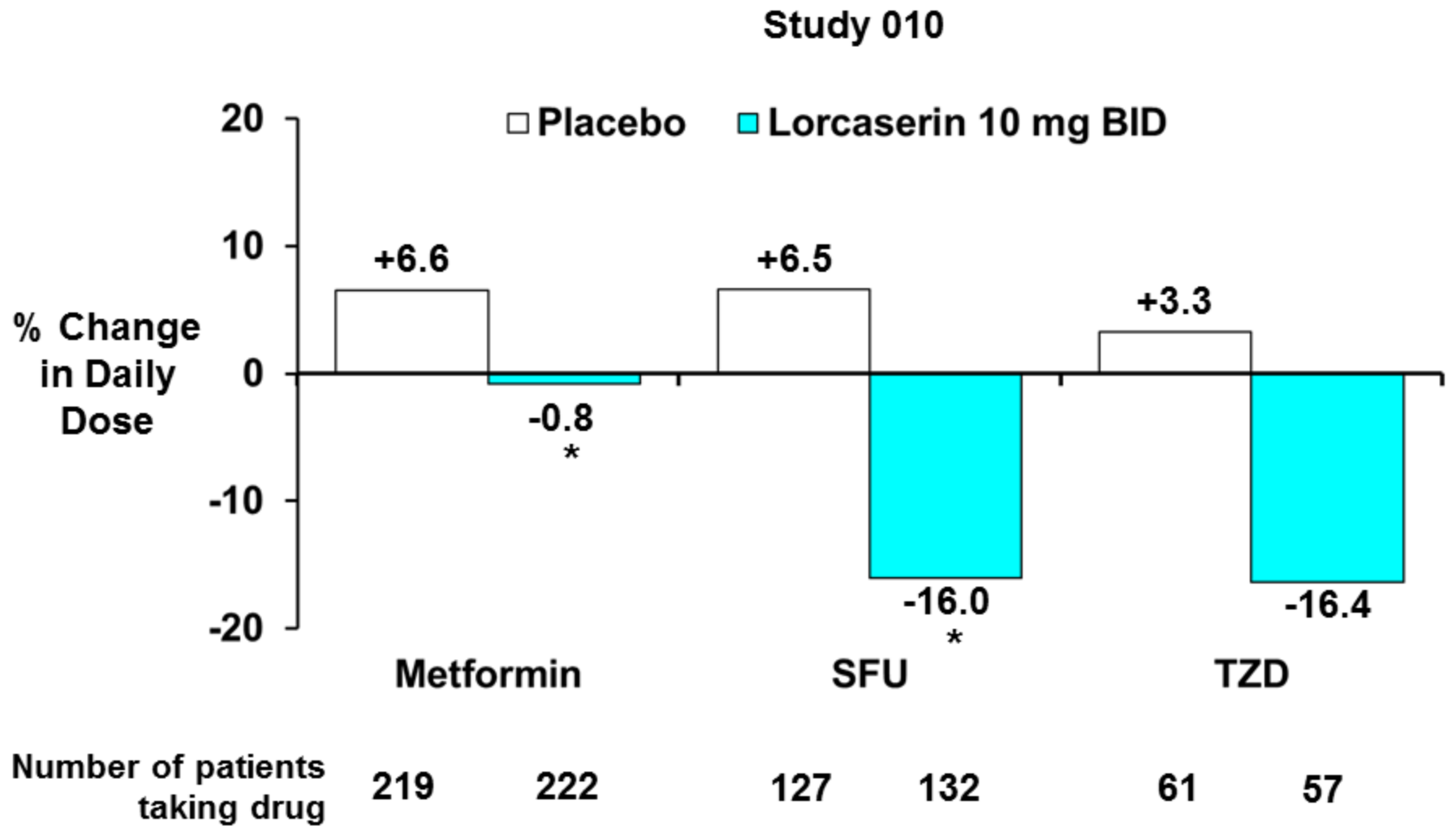
* p=0.003

Benefits to Patients with Diabetes

Lorcaserin Showed Favorable Impact on Metabolic Parameters

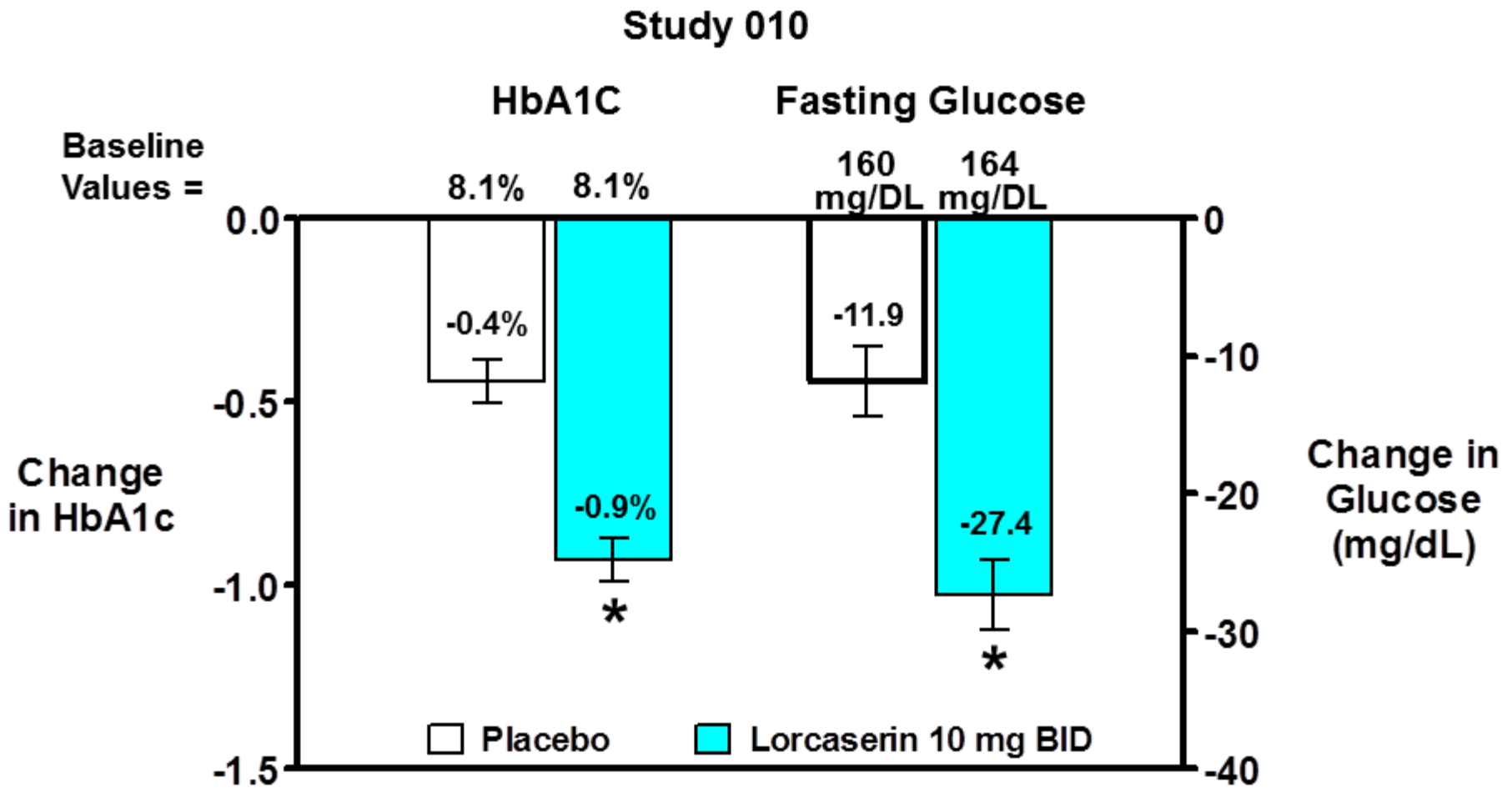


Lorcaserin Reduced Use of Anti-Diabetic Medications



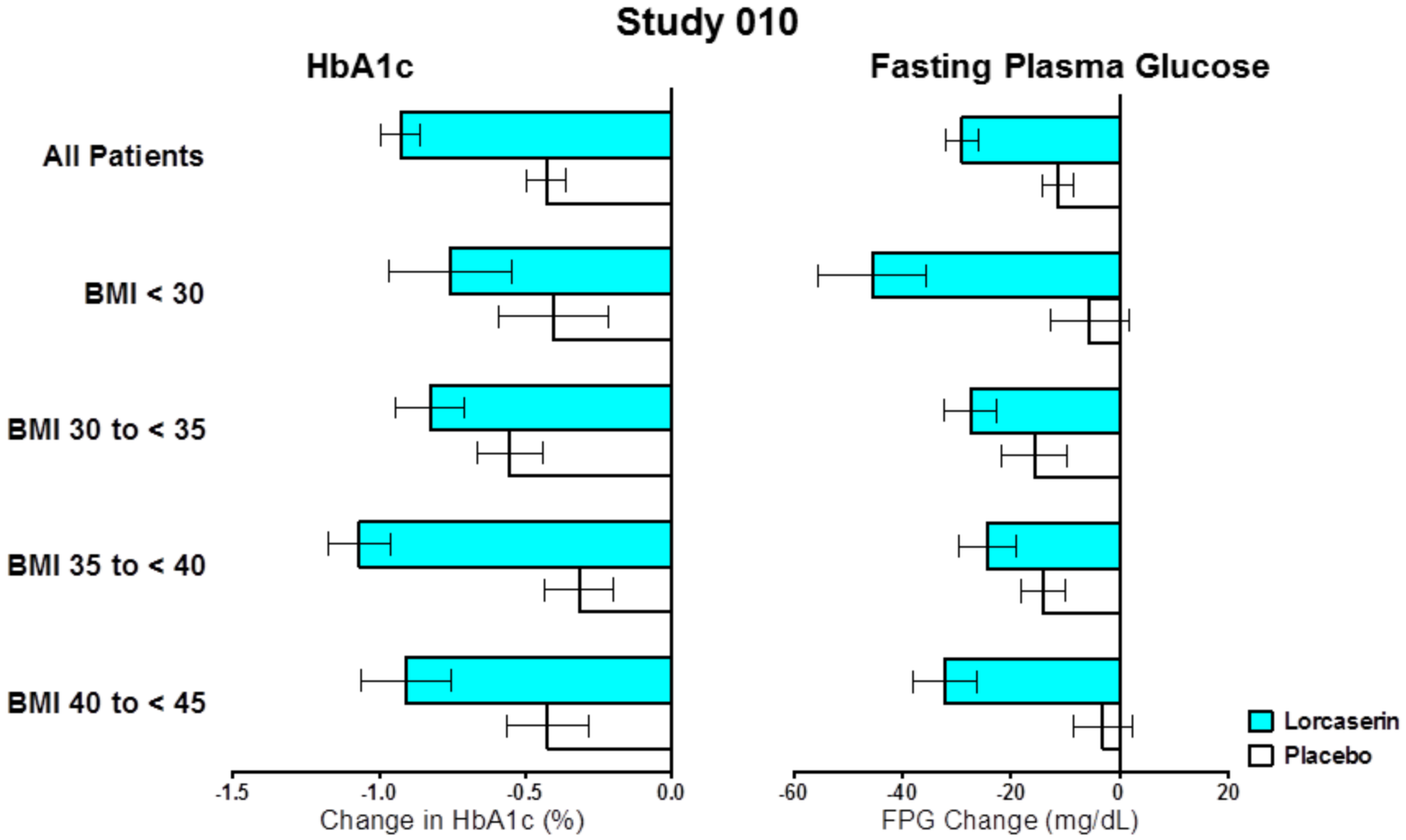
* $p < 0.05$

Lorcaserin Significantly Improved Glycemic Control at Week 52

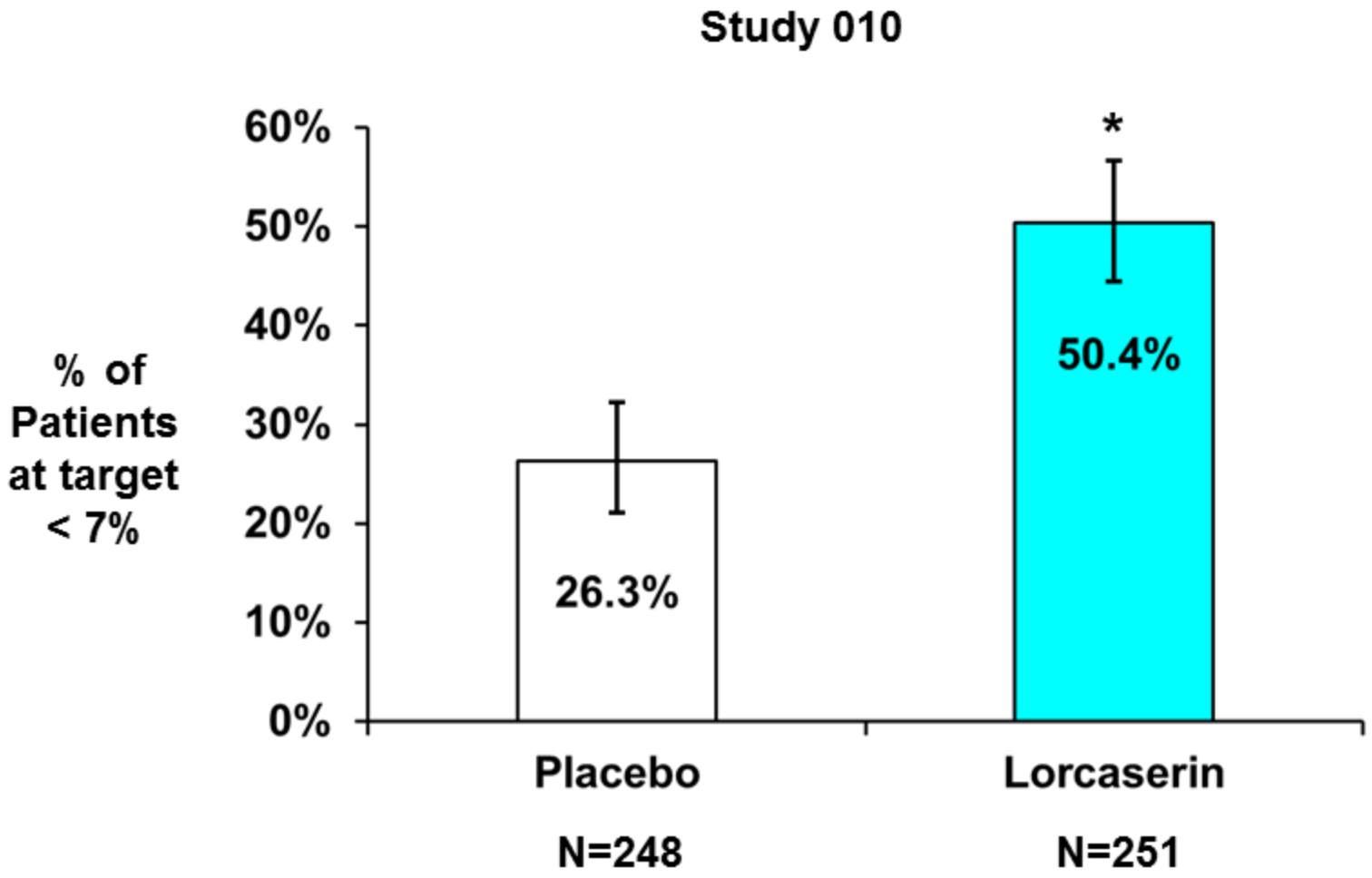


* $p < 0.001$; MITT/LOCF, LS mean $\pm$ sem; Study 010

Improved Glycemic Control Across a Range of BMIs

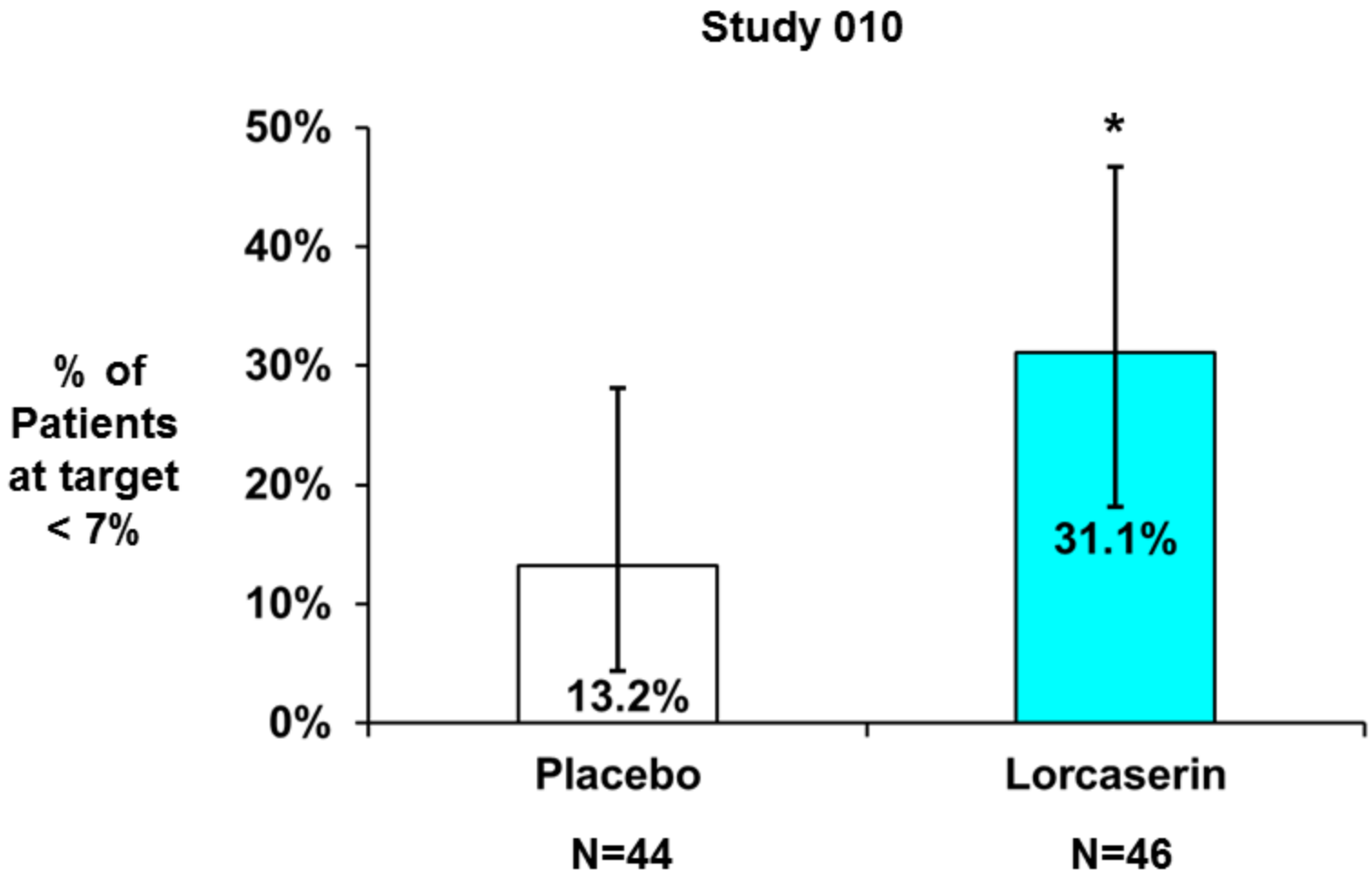


50% of Lorcaserin Patients Reached HbA1c of < 7% at Week 52



p < 0.001; MITT/LOCF; Study 010
Proportion 95%CI

31% of Patients with Baseline HbA1c ≥ 9% Decreased to < 7% at Week 52

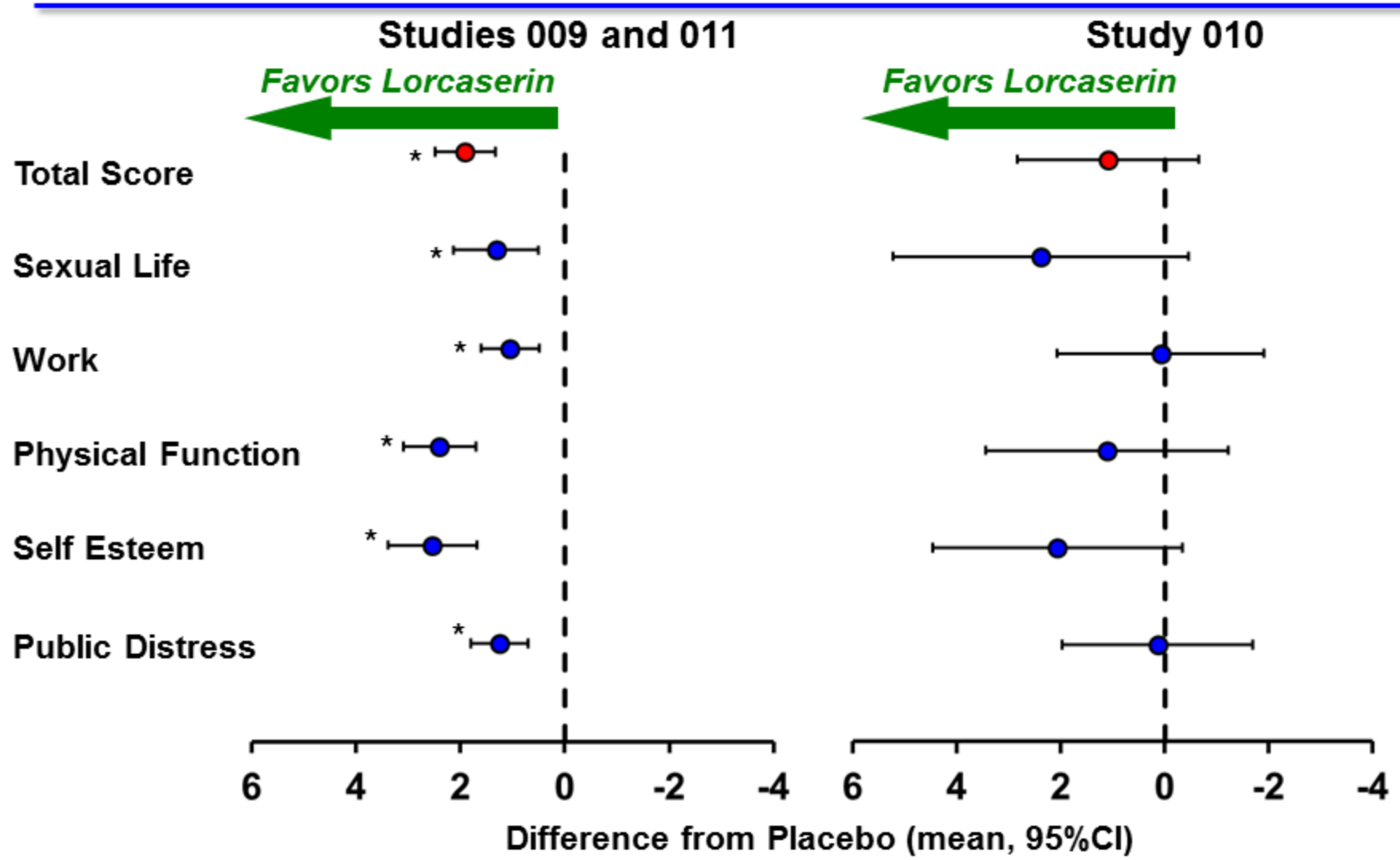


MITT/LOCF; Study 010
Proportion 95%CI

Quality of Life

IWQOL-Lite

Lorcaserin Improved Quality of Life: IWQOL-Lite Instrument

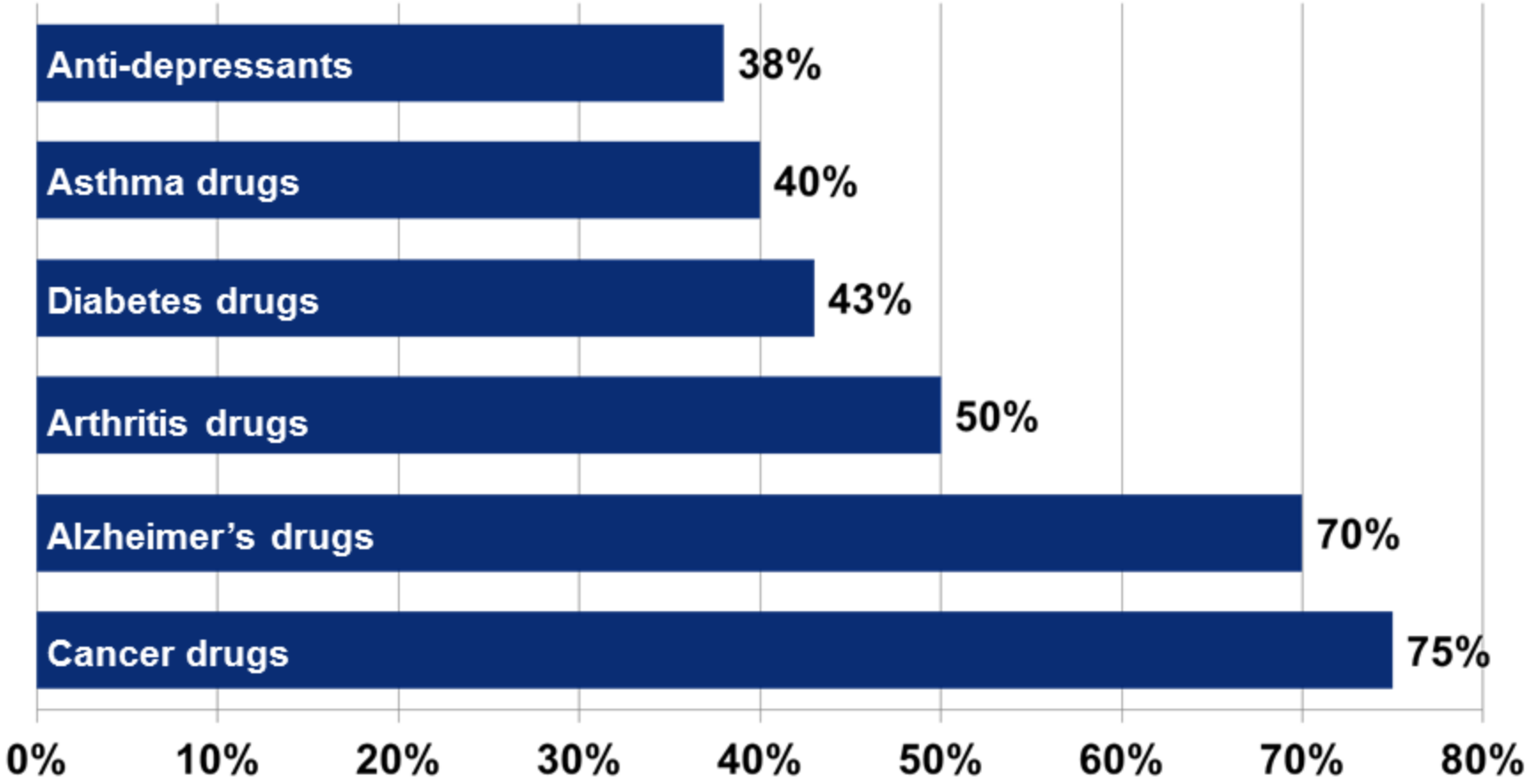


* All differences between placebo and lorcaserin were statistically significant $p < 0.001$

Responder Analysis
What Really Matters to Patients and Physicians

One Size Does Not Fit All

Percentage of the Patient Population for Which a Particular Drug is Ineffective, on Average



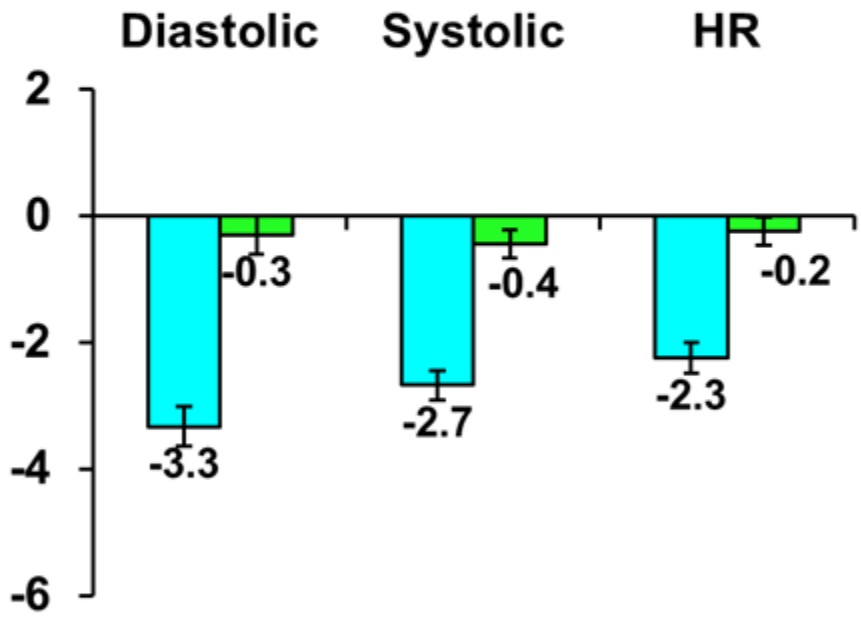
Adapted from: Spear, et al. Clinical Trends in Molecular Medicine 2001;7(5):201-204

Patients Achieving ≥ 5% Weight Loss

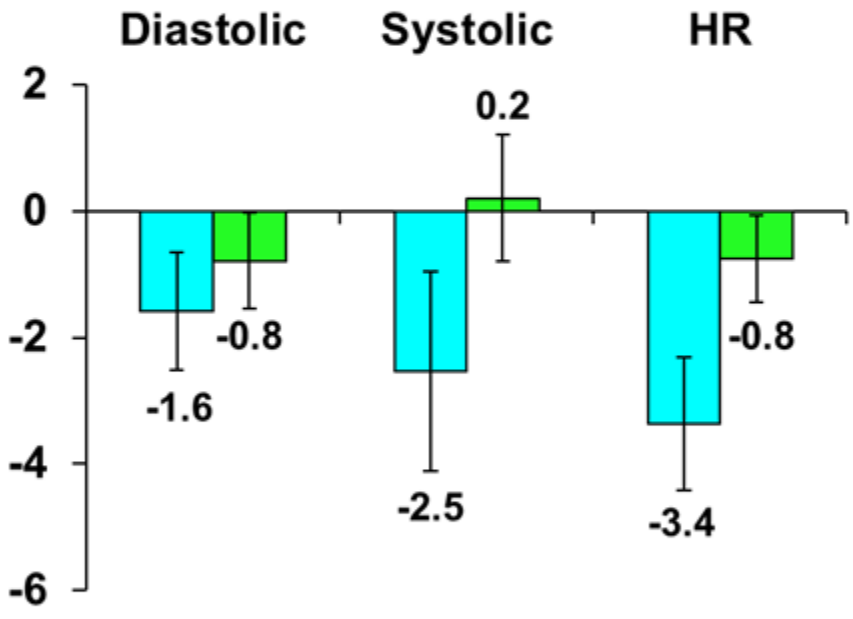
Patients achieving ≥ 5% Weight Loss	Study 009		Study 011		Study 010	
	PBO	LOR	PBO	LOR	PBO	LOR
% of ITT Population	14.2%	35.6%	18.3%	36.2%	11.5%	30.5%
% Total Weight Loss	10.7%	11.7%	11.1%	12.0%	8.9%	10.8%
Mean weight loss (lbs)	23.4	25.6	24.7	26.0	20.3	24.0
Change in BMI	-3.8	-4.2	-4.0	-4.3	-3.2	-3.8
Number of Patients	225	567	293	581	29	78

ITT-BOCF

Responder Analysis: Heart Rate, Systolic BP, and Diastolic BP



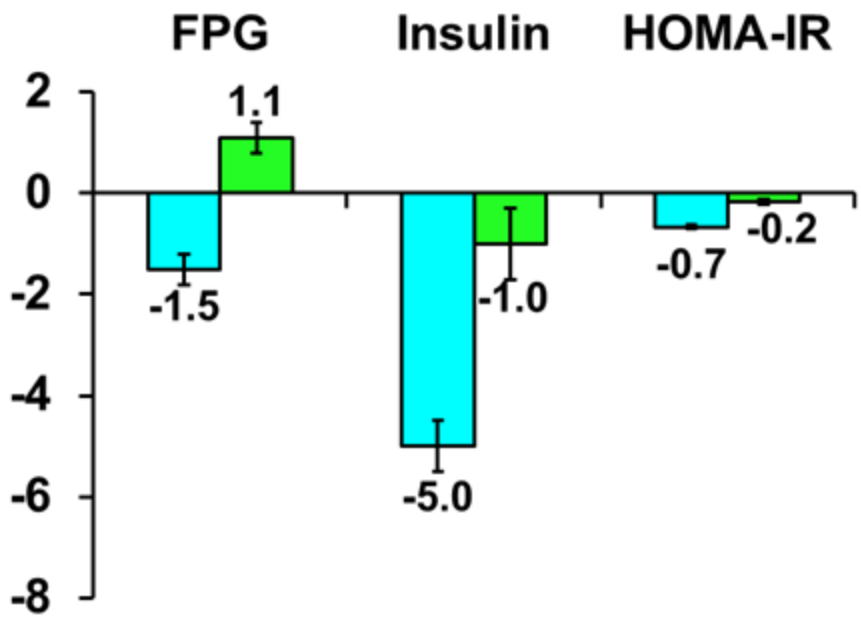
(MITT- LOCF), Studies 009 and 011



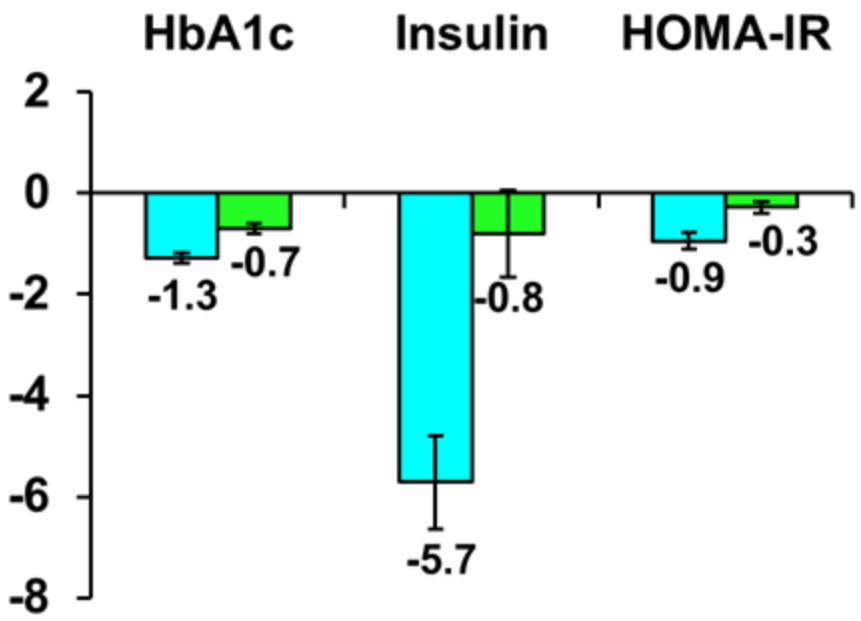
(MITT- LOCF), Study 10

Responders Non-Responders

Responder Analysis: Glycemic Parameters



(MITT- LOCF), Studies 009 and 011



(MITT- LOCF), Study 10

Responders Non-Responders

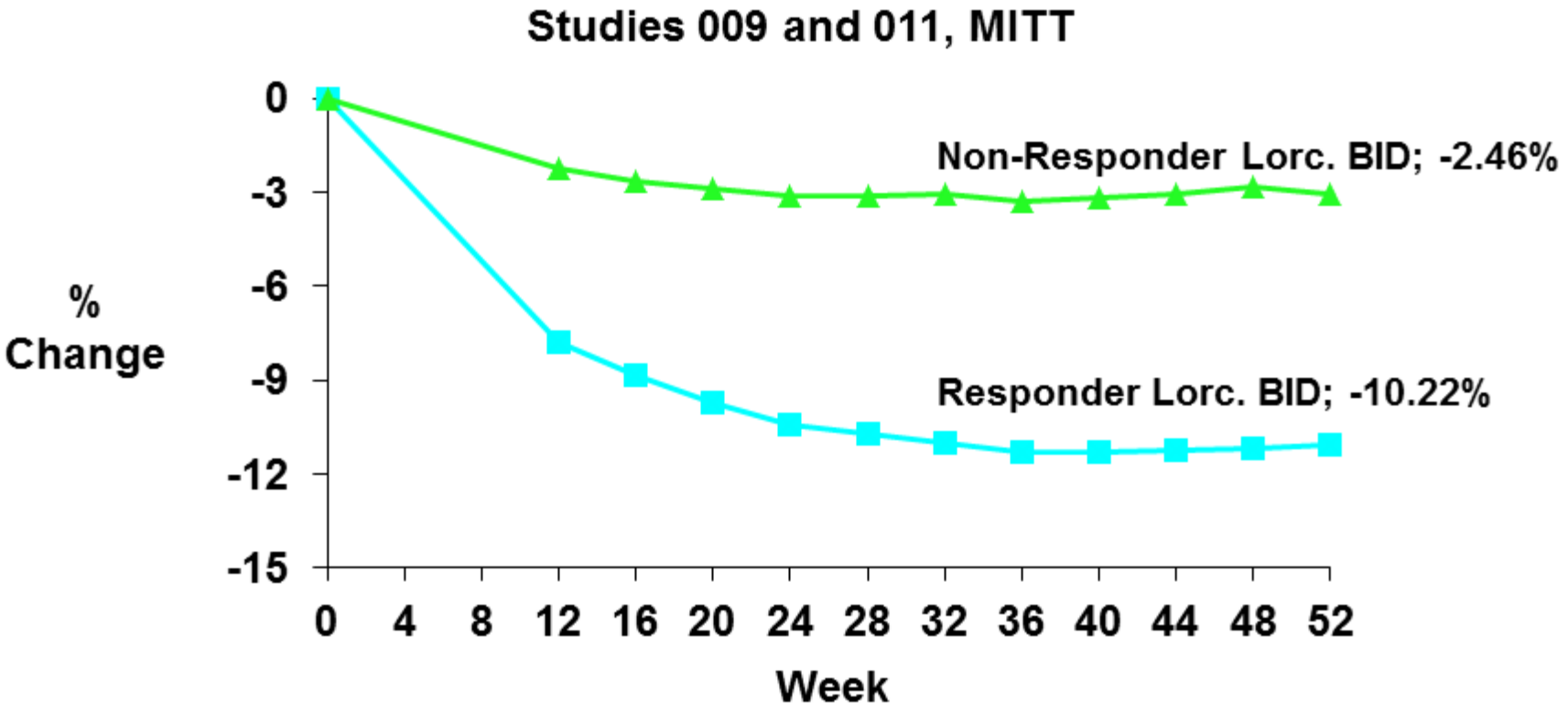
Identifying Responders

Predicting Lorcaserin Responders: How Long to Dose to Identify Non-Responders?

Week of Prediction	% Weight Loss	Sensitivity (95% CI)	Specificity (95% CI)	AUC for ROC[a]
Week 2	1.5	0.66 (0.63, 0.69)	0.63 (0.59, 0.67)	0.69
Week 4	2.5	0.75 (0.72, 0.78)	0.63 (0.58, 0.67)	0.75
Week 8	3.9	0.75 (0.72, 0.76)	0.70 (0.66, 0.74)	0.80
Week 12	4.6	0.80 (0.77, 0.83)	0.72 (0.68, 0.76)	0.85

[a] Higher number signifies better prediction.

Those Who Lost 4.5% Total Body Weight by Week 12 Were Week 52 Responders



Week 12	Completed Week 12	Completed Week 52
≥ 4.5% wt loss	1,369/3,098 (44.2%)	1,083/1,369 (79.1%)
< 4.5% wt loss	1,168/3,098 (37.7%)	680/1,168 (58.2%)

Summary and Conclusions

- We treat weight loss to
  - Reduce cardiovascular risk
  - Prevent diabetes / improve glycemic control
  - Provide benefits important to individual health
- Lorcaserin → clinically meaningful weight loss
  - Improvements in CV and metabolic risk biomarkers
  - Improvements in HbA1c and FPG
  - Approx. 1/3 of patients lost 11% or 25 lbs

Arena

Review of Safety

William Shanahan, MD
Sr. Vice President & Chief Medical Officer
Arena Pharmaceuticals

Overall Summary of AEs

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lor BID n=3,195	Placebo n=252	Lor BID n=256
	YEAR 1			
Any AE	75.5%	82.8%	84.5%	92.2%
Any SAE	2.3%	2.7%	6.7%	6.3%
Dropouts due to AE	5.6%	7.1%	4.3%	8.6%
	YEAR 2			
Any AE	73.9%	78.5%	--	--
Any SAE	3.2%	2.6%	--	--
Dropouts due to AE	2.7%	3.7%	--	--
Death, n (%)*	2 (0.06%)	0	--	--

* 1 death during Year 2: patient on placebo in Year 2, lorcaserin in Year 1

AEs with Lorcaserin Incidence ≥ 1% Over Placebo (Based on 009 and 011 incidence)

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Headache	10.1%	16.8%	7.1%	14.5%
Upper respiratory infection	12.3%	13.7%	14.7%	13.7%
Dizziness	3.8%	8.5%	6.3%	7.0%
Nausea	5.3%	8.3%	7.9%	9.4%
Fatigue	3.6%	7.2%	4.0%	7.4%
Urinary tract infection	5.4%	6.5%	6.0%	9.0%
Constipation	3.9%	5.8%	4.8%	4.3%
Dry mouth	2.3%	5.3%	1.2%	1.6%
Viral gastroenteritis	3.2%	4.3%	4.4%	7.0%
Vomiting	2.6%	3.8%	3.6%	3.5%
Oropharyngeal pain	2.5%	3.5%	4.8%	4.3%

Discontinuations due to AEs ≥ 0.4% in Studies 009 and 011 or > 2 Patients in Study 010

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Any Withdrawal for AE	5.6%	7.1%	4.3%	8.6%
Headache	0.8%	1.3%	0	0.4%
Depression	0.5%	0.9%	0	0.8%
Dizziness	0.2%	0.7%	0	0.4%
Nausea	0.4%	0.7%	0	0
Anxiety	0.3%	0.4%	0.8%	0

SAEs: Lorcaserin Incidence > Placebo and > 2 Patients; Year 1

	Pooled Studies 009 and 011		Study 010	
	Placebo n=3,185	Lorcaserin 10 mg BID n=3,195	Placebo n=252	Lorcaserin 10 mg BID n=256
Any SAE	2.3%	2.7%	6.7%	6.3%
Cholecystitis/cholelithiasis	0.2%	0.3%	0	0.4%
Cellulitis	< 0.1%	0.1%	0.8%	0
Intervertebral disc protrusion	0.1%	0.1%	0	0.4%
Myocardial infarction	0	0.1%	0.8%	0

Post Hoc Cardiovascular Clinical Events Committee Adjudication of SAEs in Studies 009 and 011

Adjudicated AE Term	Placebo N=3,185	Lorcaserin 10 mg BID N=3,195	Lorcaserin 10 mg QD N=801	Lorcaserin/ Placebo Yr 2 N=1,553
Unstable angina	2	1	0	1
MI, spontaneous	0	4	0	0
MI, silent	1	0	0	0
Stroke, ischemic	1	0	0	0
TIA	2	0	0	0
Total cardiac	3	5	0	1
Overall Total	6	5	0	1

Abbreviations: MI = myocardial infarction; TIA = transient ischemic attack

SAEs of Ischaemic Heart Disease and Cerebrovascular Disorders: Not Adjudicated for MACE; Study 010

		Lorcaserin 10 mg	
	Placebo	BID	QD
	N=252	N=256	N=95
Preferred Term	n	n	n
Number of patients with any SAE	2	1	4
Coronary artery occlusion	0	1	0
Myocardial infarction	2	0	0
Angina pectoris	0	0	1
Coronary artery disease	0	0	1
Total Cardiac	2	1	2
Cerebrovascular accident	0	0	2

CV Safety Assessment

- No identified CV safety signal for lorcaserin
- EMDAC meeting on March 28-29 provided recommendations for CV safety studies for obesity drugs
- We are committed to working with the FDA to design appropriate post-marketing studies to assess CV safety as necessary

Arena

Echocardiographic Safety Evaluation of Cardiac Valve Function

FDA-Defined Valvulopathy

- Aortic and Mitral Regurgitation
  - Rated from absent to severe
- FDA defines significant valvular regurgitation as:

MILD or greater aortic regurgitation

OR

MODERATE or greater mitral regurgitation

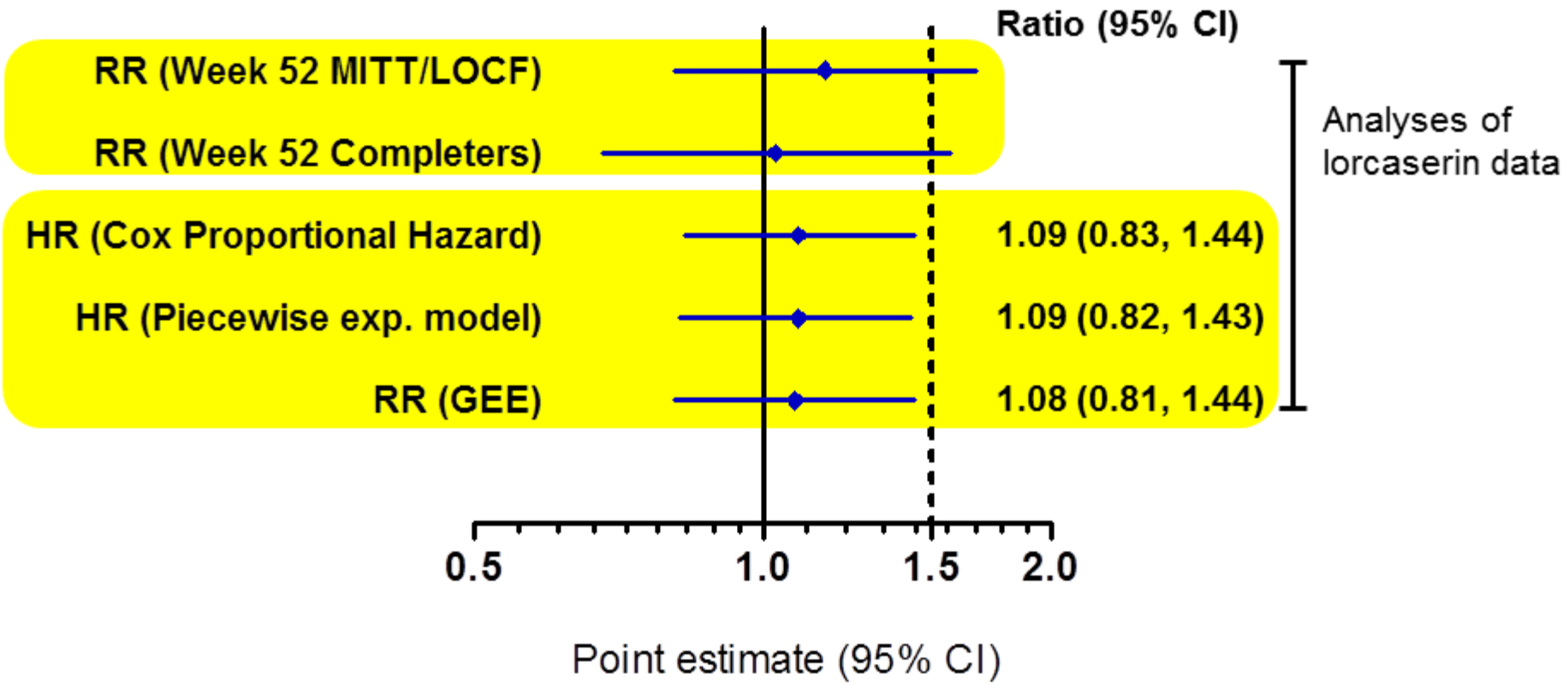
Cardiac Valvular Function Assessed by Serial Echocardiographs

- > 20,000 echocardiographs
- 7,800 patients
- Evaluated at baseline or screening, and every 6 months thereafter
- 426 patients received lorcaserin BID for 2 years

Cardiac Valvular Function

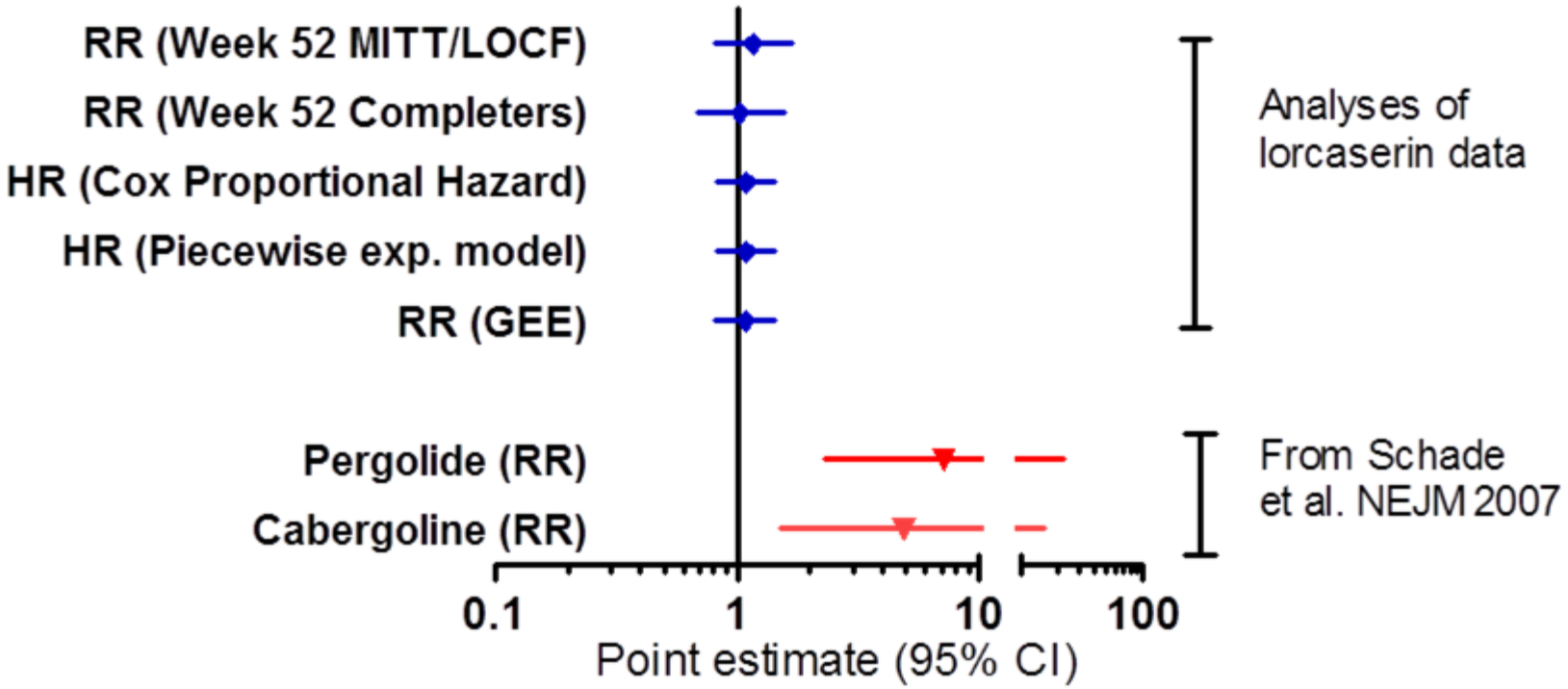
- Week 52 rates of valvulopathy
  - Lorcaserin = 2.37%
  - Placebo = 2.04%

Risk Analyses for FDA-defined Valvulopathy Phase 3 Studies



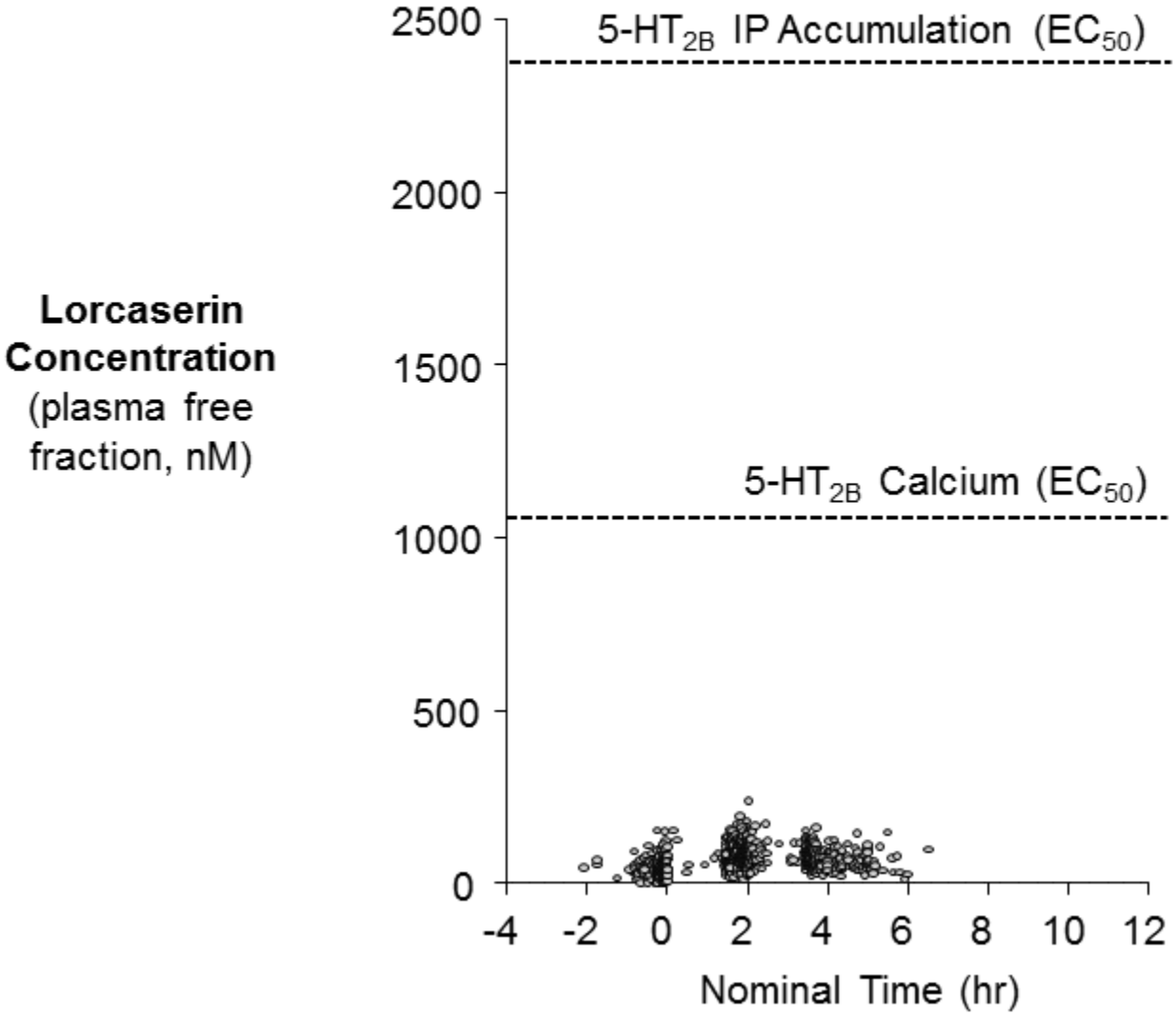
RR = relative risk; HR = hazard ratio;
GEE = generalized estimating equations

Risk Analyses for FDA-Defined Valvulopathy Phase 3 Studies

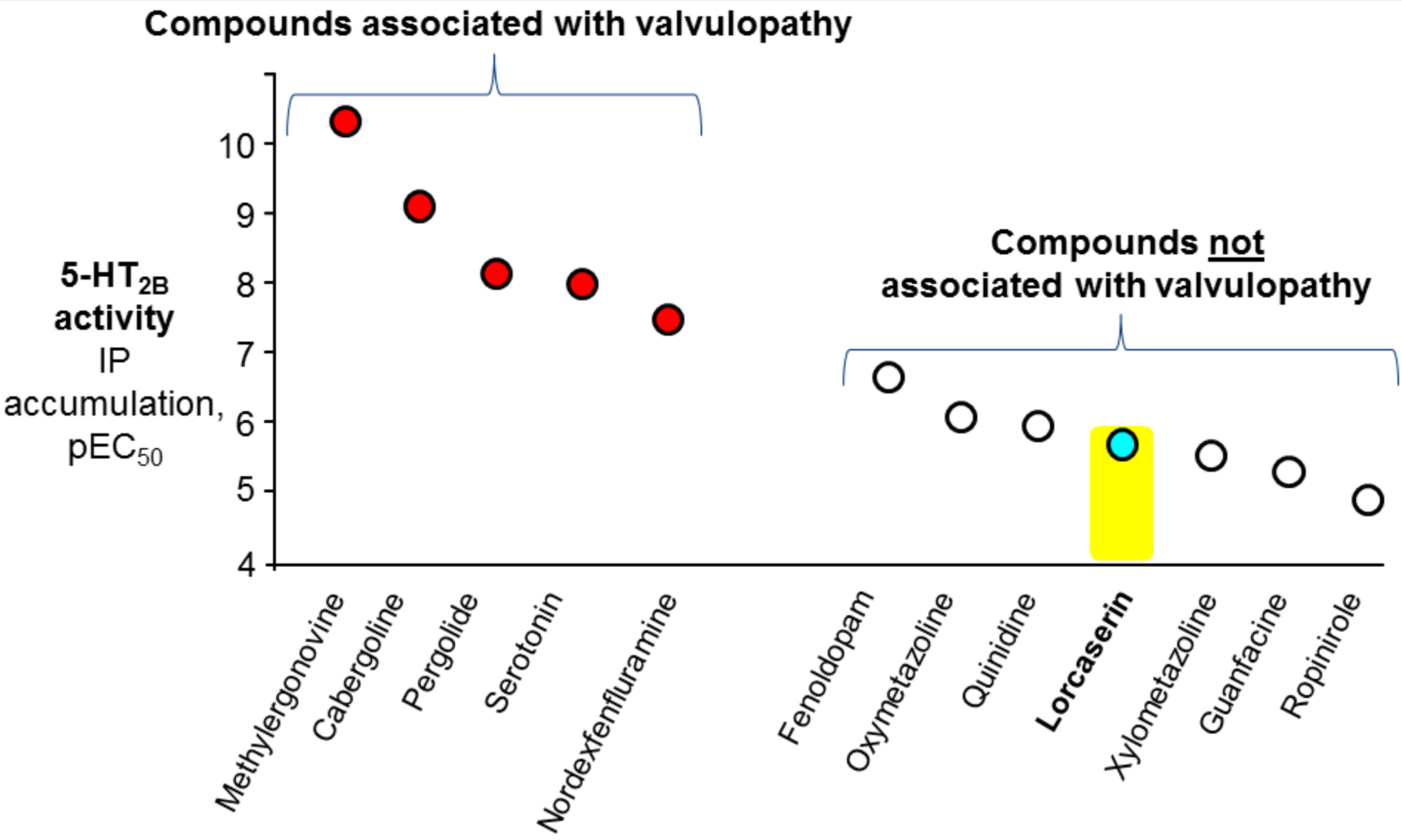


RR = relative risk; HR = hazard ratio;
GEE = generalized estimating equations

Lorcaserin Does Not Activate 5-HT$_{2B}$ Receptors at the MRD



Lorcaserin is Not Associated with Valvulopathy



Valvulopathy Summary

- Appropriately powered risk ratio analyses rule out a 1.5 fold or greater incidence of FDA valvulopathy with lorcaserin treatment for up to 2 years
- Receptor pharmacology studies strongly suggest that lorcaserin will not activate the 5-HT2B receptor at therapeutic doses

Clinical Summary

- Medically meaningful weight loss in three phase 3 trials
  - Improvements in anthropometric, cardiovascular and quality of life parameters
  - Significant weight loss in patients with type 2 diabetes
    - Improvements in glycemic control: HbA1c, fasting glucose, and use of medications to treat diabetes
- Safety data across all studies are consistent

Arena

Preclinical Safety: Mammary Tumors and Astrocytoma

Dominic Behan, PhD
Exec. Vice President & Chief Scientific Officer
Arena Pharmaceuticals

Lorcaserin Carcinogenicity Program

- Genotoxicity assays negative
- 2-Year carcinogenicity in mice
  - No lorcaserin-related tumors
- 2-Year carcinogenicity in Sprague-Dawley rats
  - Astrocytoma in males at high dose
  - Mammary tumors in females

Assessing Relevance of Tumor Findings in Rodents

- Two ways to establish a rodent tumor is reasonably irrelevant to human risk
  - Safety margin:
    Drug exposure level needed to cause the tumor in rodents is substantially greater than human exposure at recommended dose
  - Rodent specific mechanism
- Either is sufficient

Lorcaserin CNS Exposure to Determine Safety Margin

- Brain/CSF ratios were consistent across multiple preclinical species
- CSF lorcaserin exposure was measured in healthy obese subjects
- Human brain exposure was extrapolated using mean CSF-brain ratios in preclinical species
- Safety margin for astrocytoma is based on predicted brain exposure in humans

Astrocytoma in Male Rats: Brain Exposure Margin ≥ 70X

	Lorcaserin Dose (mg/kg/day)			
	Vehicle	10	30	100
Brain exposure margin	-	**70**	**360**	**> 360**
Number of Animals	65	65	65	75
n with astrocytoma	1	0	4	8*
% with astrocytoma	1.5	0	6.2	10.7

* $p < 0.01$ vs. vehicle

Independent Pathology Working Group Establishes Diagnostic Certainty

- Blinded re-adjudication of tissues
- Fibroadenoma easily distinguished from Adenocarcinoma
- Unanimous adjudication:
  - Adenocarcinoma = 93%
  - Fibroadenoma = 97%
- Diagnostic certainty established
- Considered the definitive data set

≥ 24-Fold Margin for Adenocarcinoma in Female Rats

	Lorcaserin Dose (mg/kg/day)			
	Vehicle	10	30	100
Plasma exposure margin	-	7	24	82
Number of Animals	65	65	65	75
n with adenocarcinoma	26	21	24	51*
% with adenocarcinoma	40%	32%	37%	68%*

* Statistically significant vs. control ($p < 0.001$)

Safety Margins for Lorcaserin

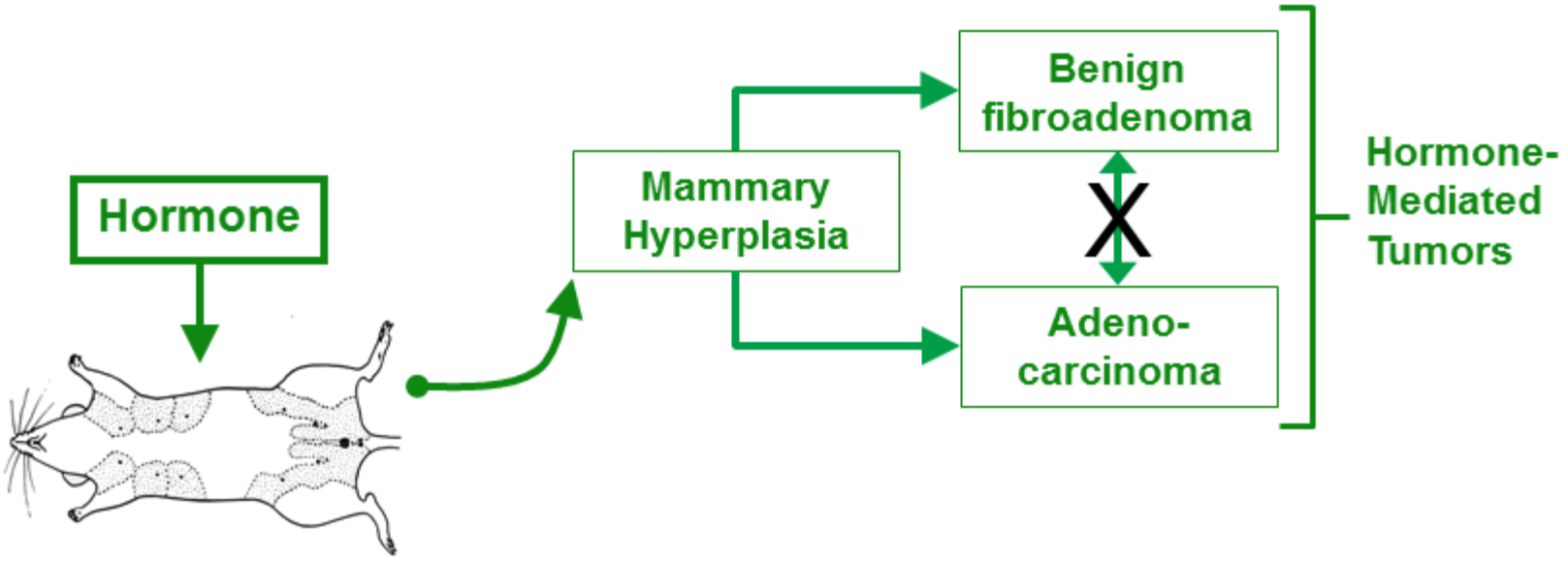
- Safety margin ≥ 70 times human exposure for astrocytoma in male rats
- Safety margin ≥ 24 times human exposure for mammary adenocarcinoma in female rats

Incidence of Mammary Fibroadenoma in Female Rats

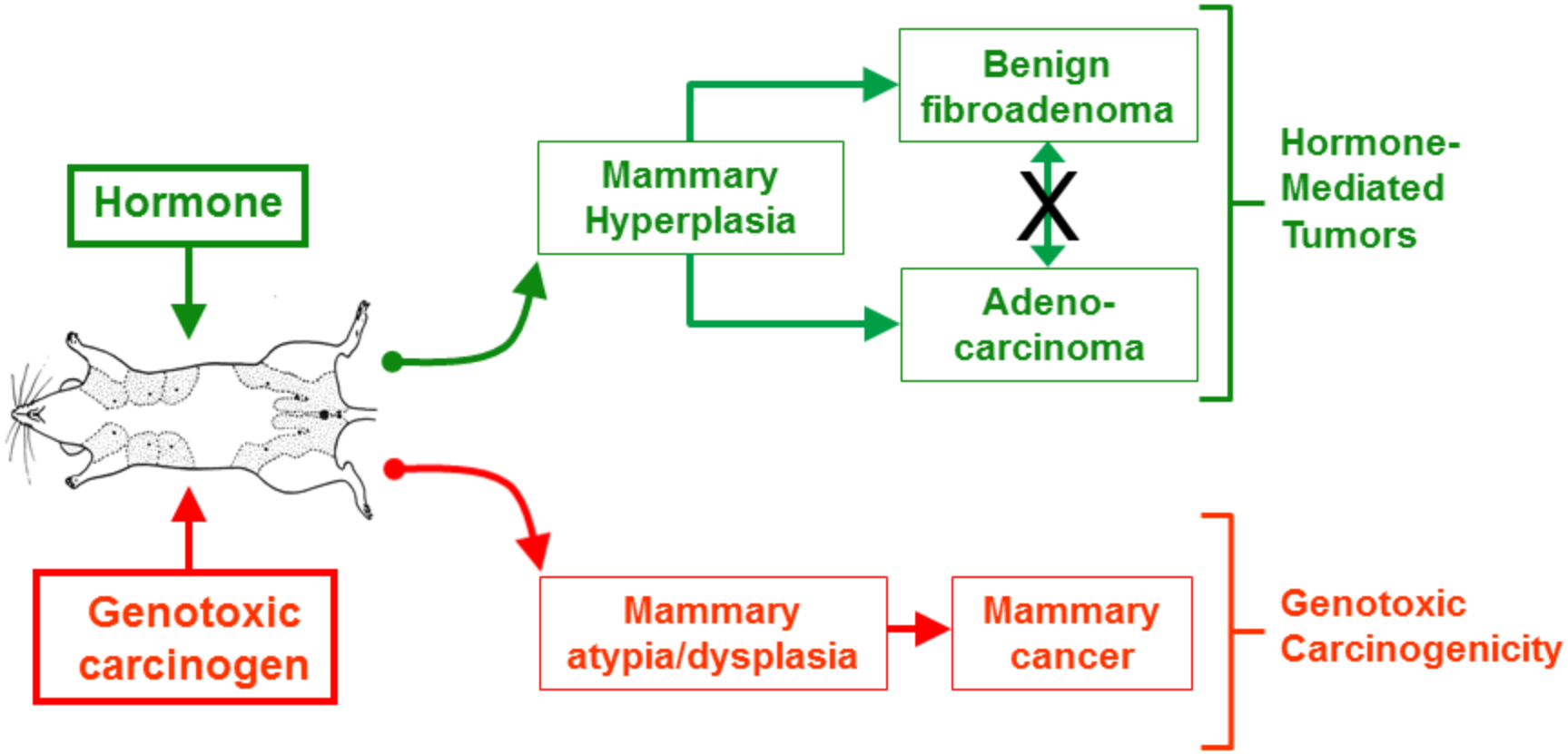
	Lorcaserin Dose (mg/kg/day)			
	Vehicle	10	30	100
Plasma exposure margin	-	**7**	**24**	**82**
Number of Animals	65	65	65	75
n with fibroadenoma	24	54	55	51
% with fibroadenoma	37%	83%*	85%*	68%*

* Statistically significant vs. control ($p < 0.001$)

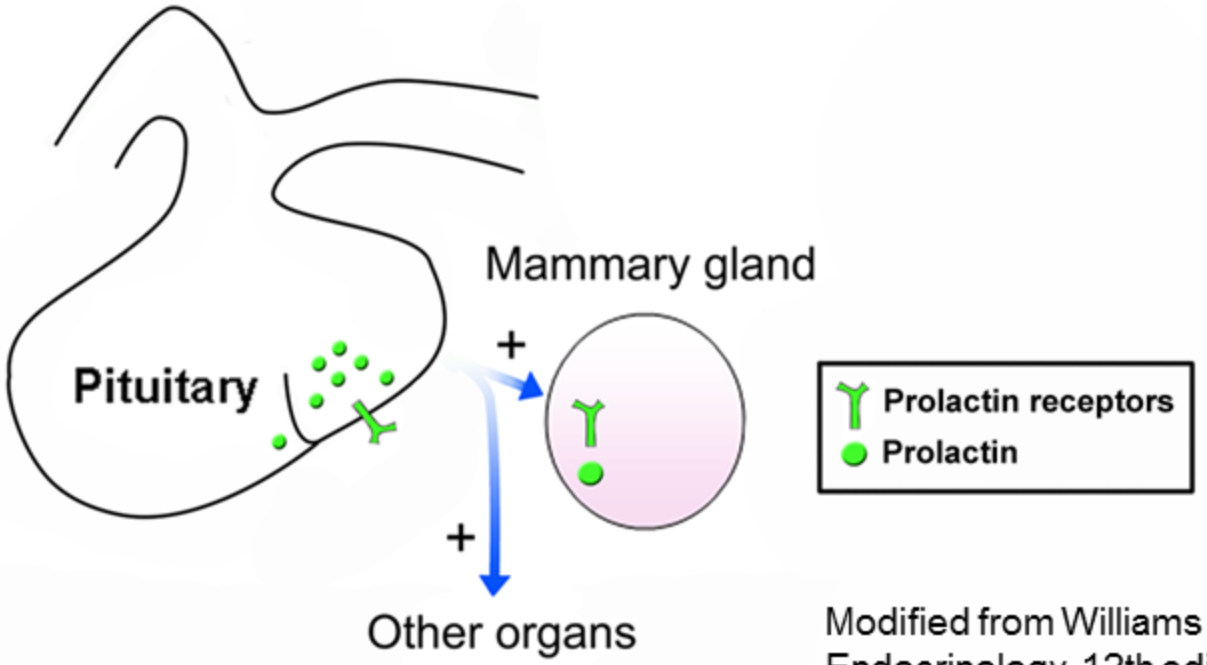
Two Pathways to Mammary Tumors in the Female Rat



Two Pathways to Mammary Tumors in the Female Rat

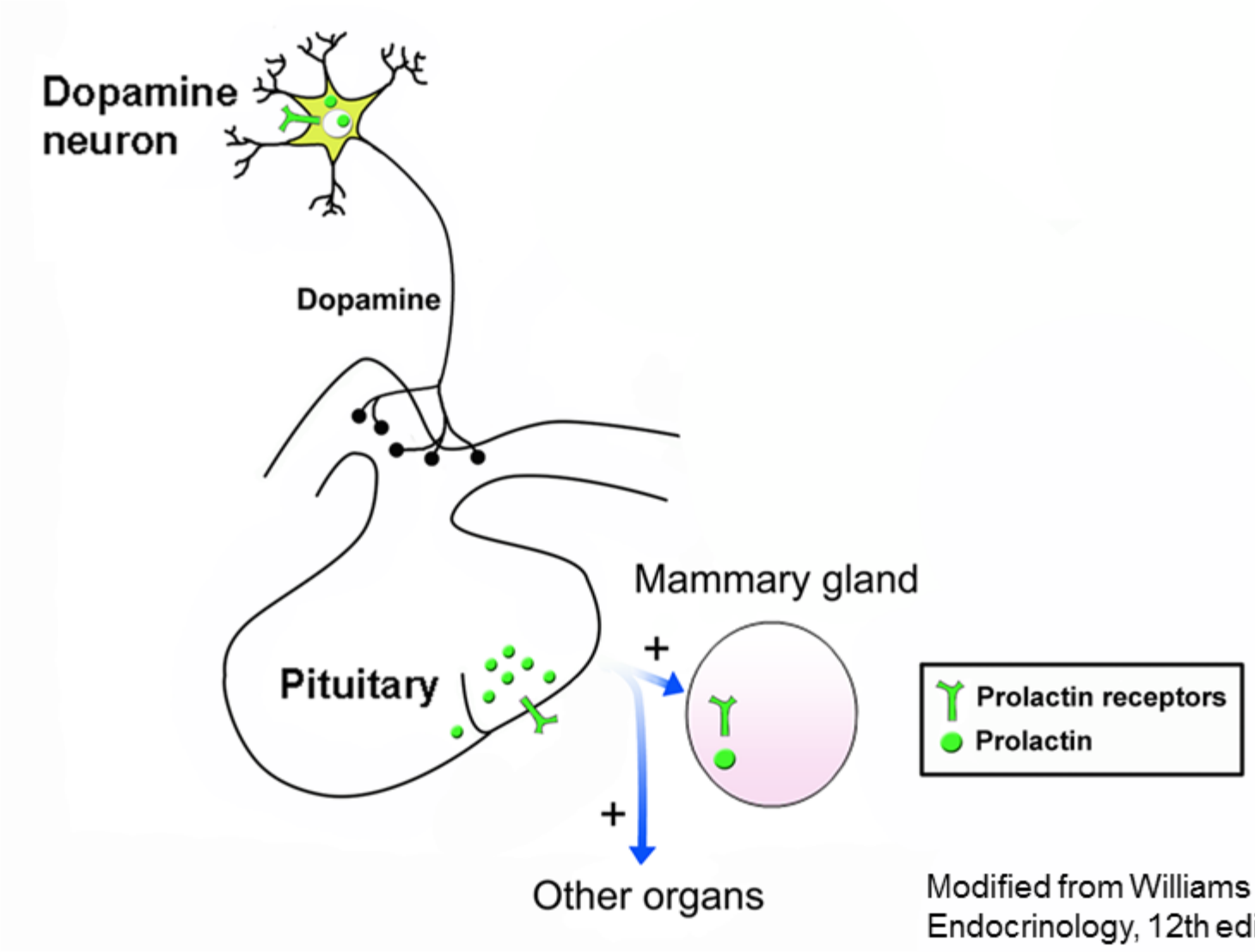


Control of Pituitary Prolactin Release by Dopaminergic and Serotonergic Mechanisms



Modified from Williams Textbook of Endocrinology, 12th edition, 2011

Control of Pituitary Prolactin Release by Dopaminergic and Serotonergic Mechanisms



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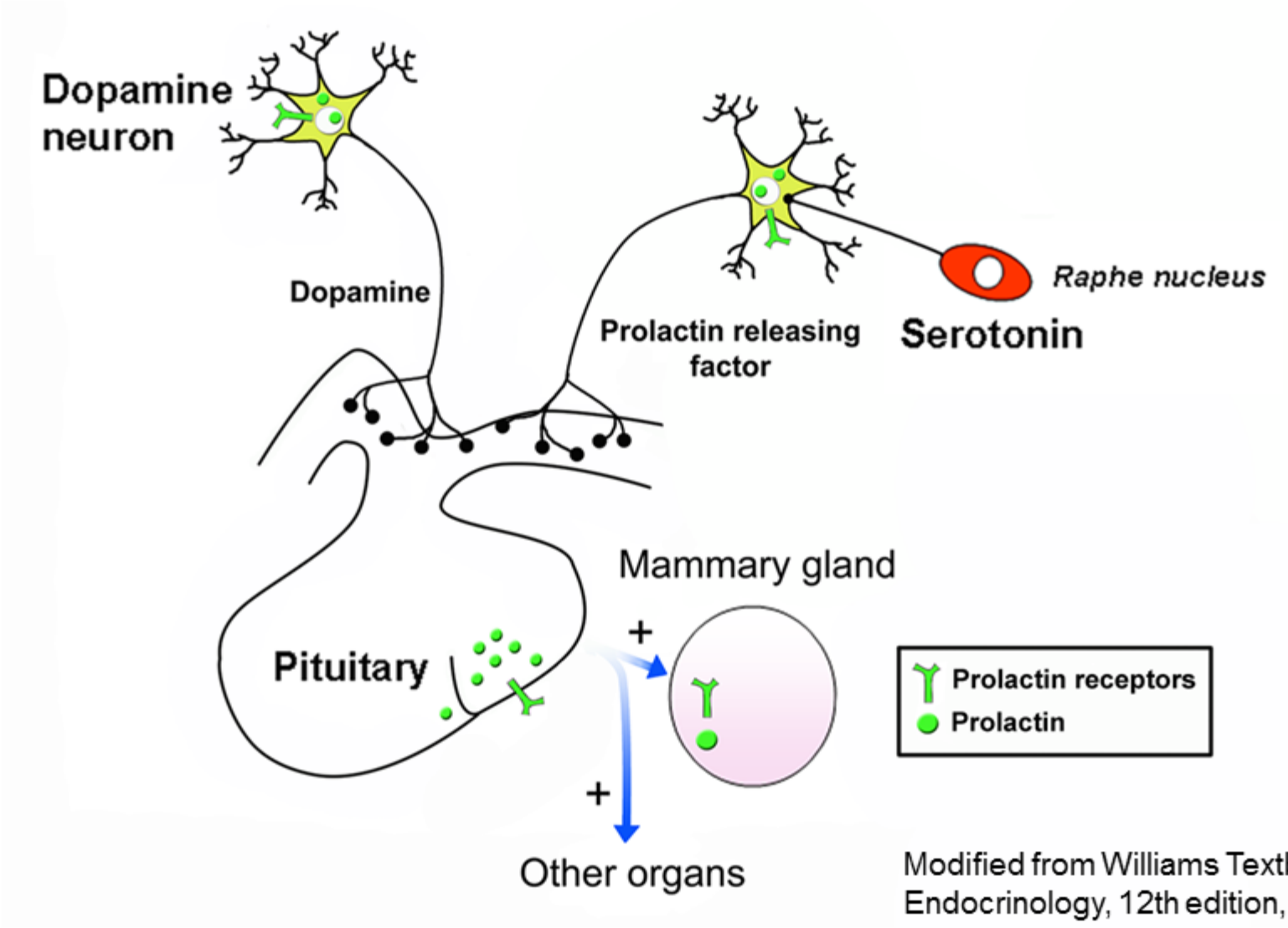
Control of Pituitary Prolactin Release by Dopaminergic and Serotonergic Mechanisms



Modified from Williams Textbook of Endocrinology, 12th edition, 2011

Prolactin (PRL) Dependence of Benign and Malignant Mammary Tumors in Rats

- Dopamine D_2 blockers:
  - Markedly and chronically increase circulating prolactin
  - Increase rat mammary tumors
- Smaller and shorter duration prolactin increases are relevant to tumor formation

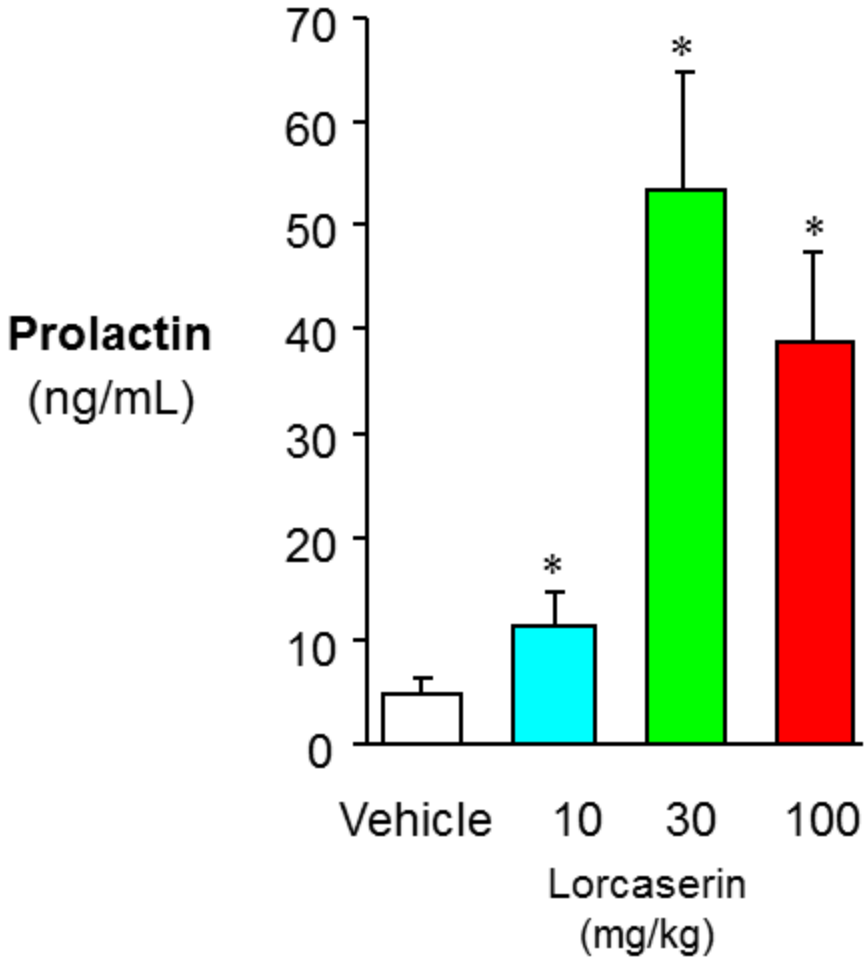
Rationale for Rat Mechanistic Studies

1. **Does lorcaserin increase prolactin?**
   - Female rats dosed for up to three months: Prolactin measured in plasma and pituitary

2. **Does treatment with lorcaserin cause measurable changes in mammary tissue?**
   - Multiple mammary tissue endpoints assessed in three month studies

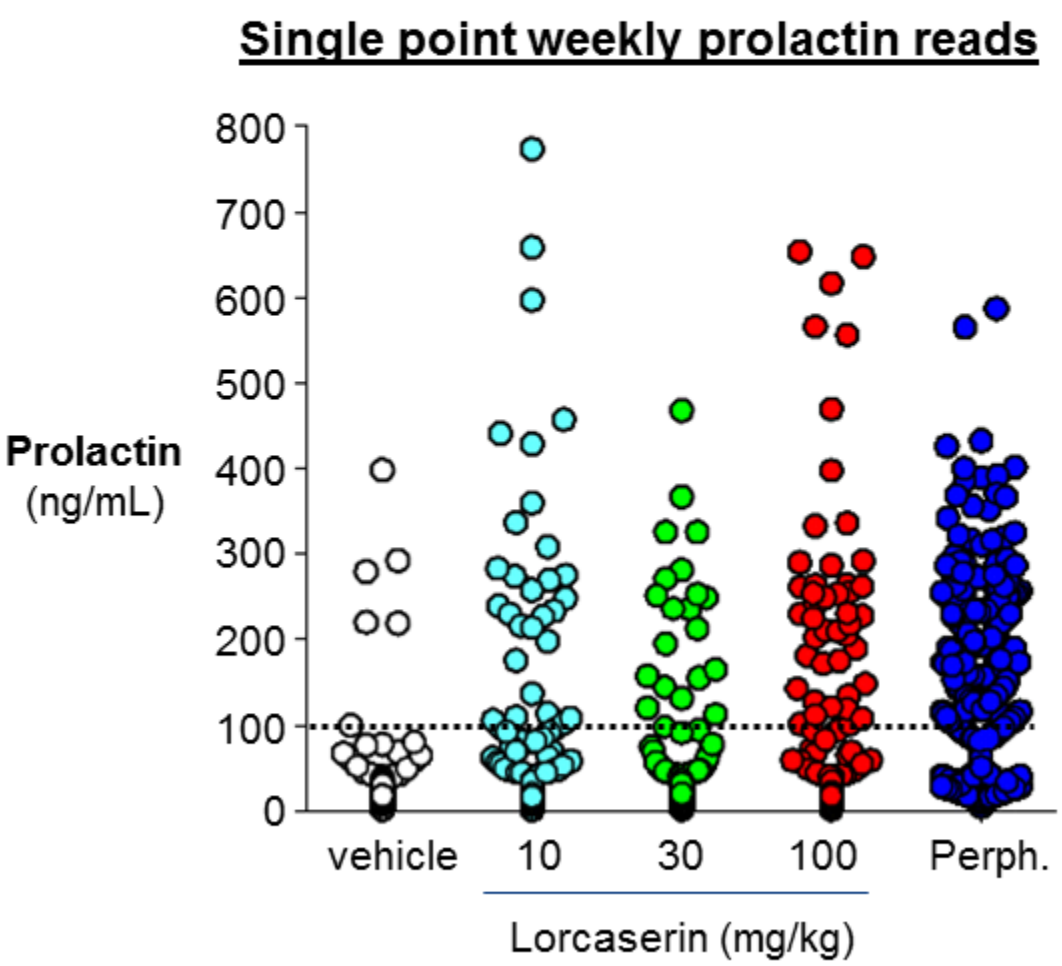
3. **Can prolactin be linked to lorcaserin-induced mammary tissue changes?**
   - Effect of pituitary removal and prolactin receptor blockade on lorcaserin-induced mammary changes measured.

Lorcaserin Dose-Dependently Increases Serum Prolactin in Female Rats



n = 25 per group
* p < 0.01 vs. vehicle

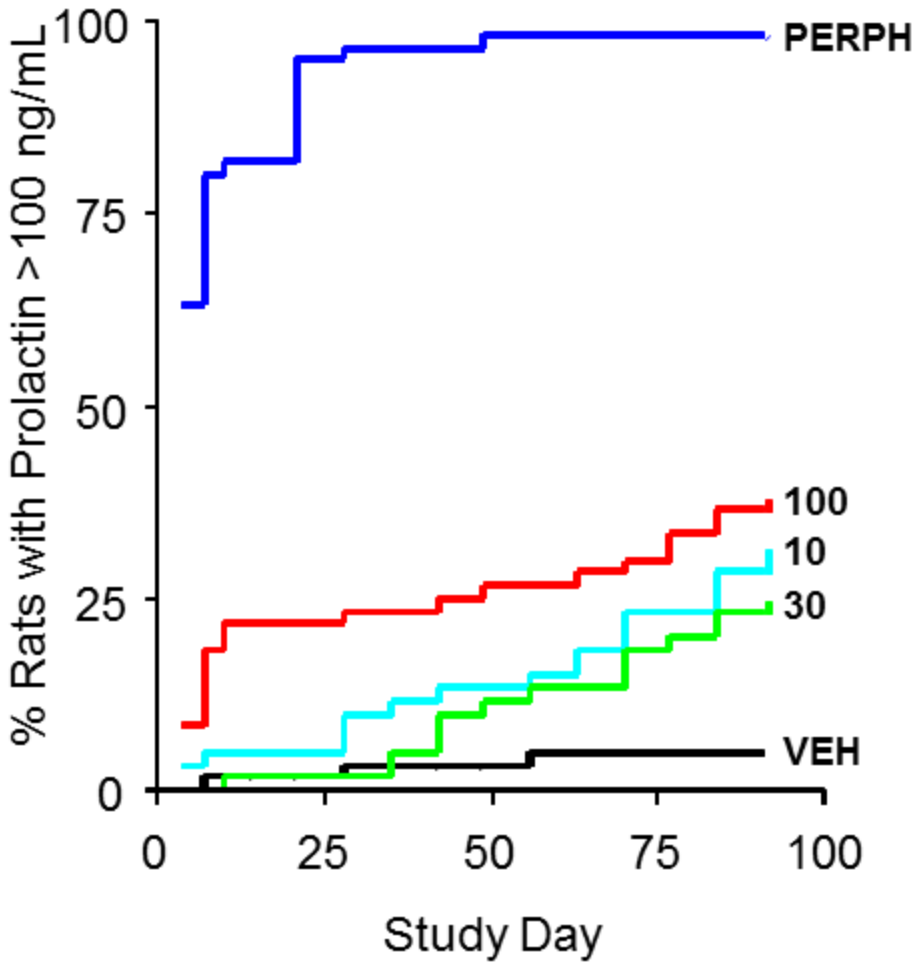
Lorcaserin Increases Plasma Prolactin During a Three-Month Study



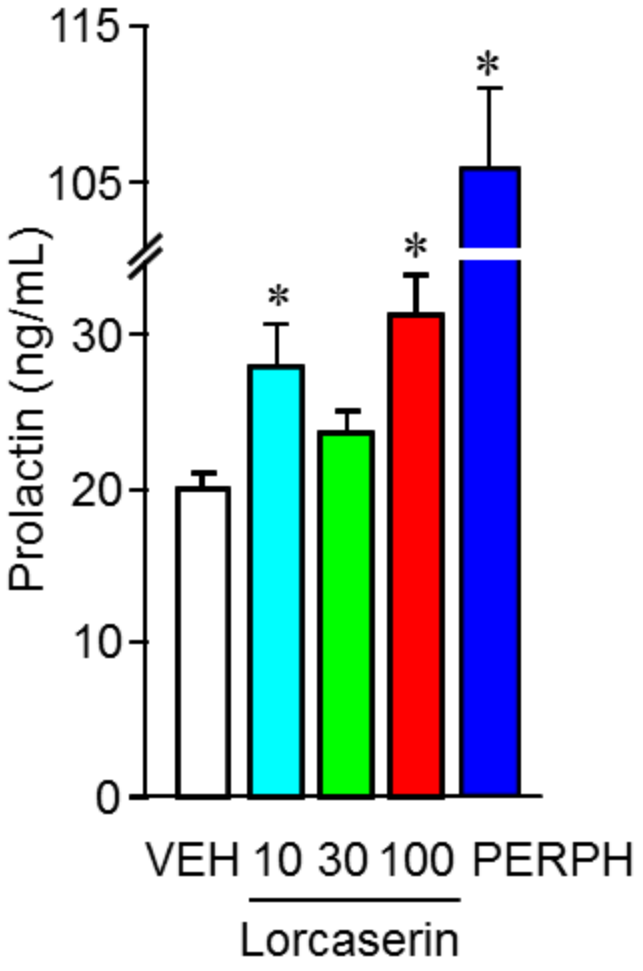
All n = 56-60 per group

Lorcaserin Increases Plasma Prolactin During a Three-Month Study

Time to first high prolactin event

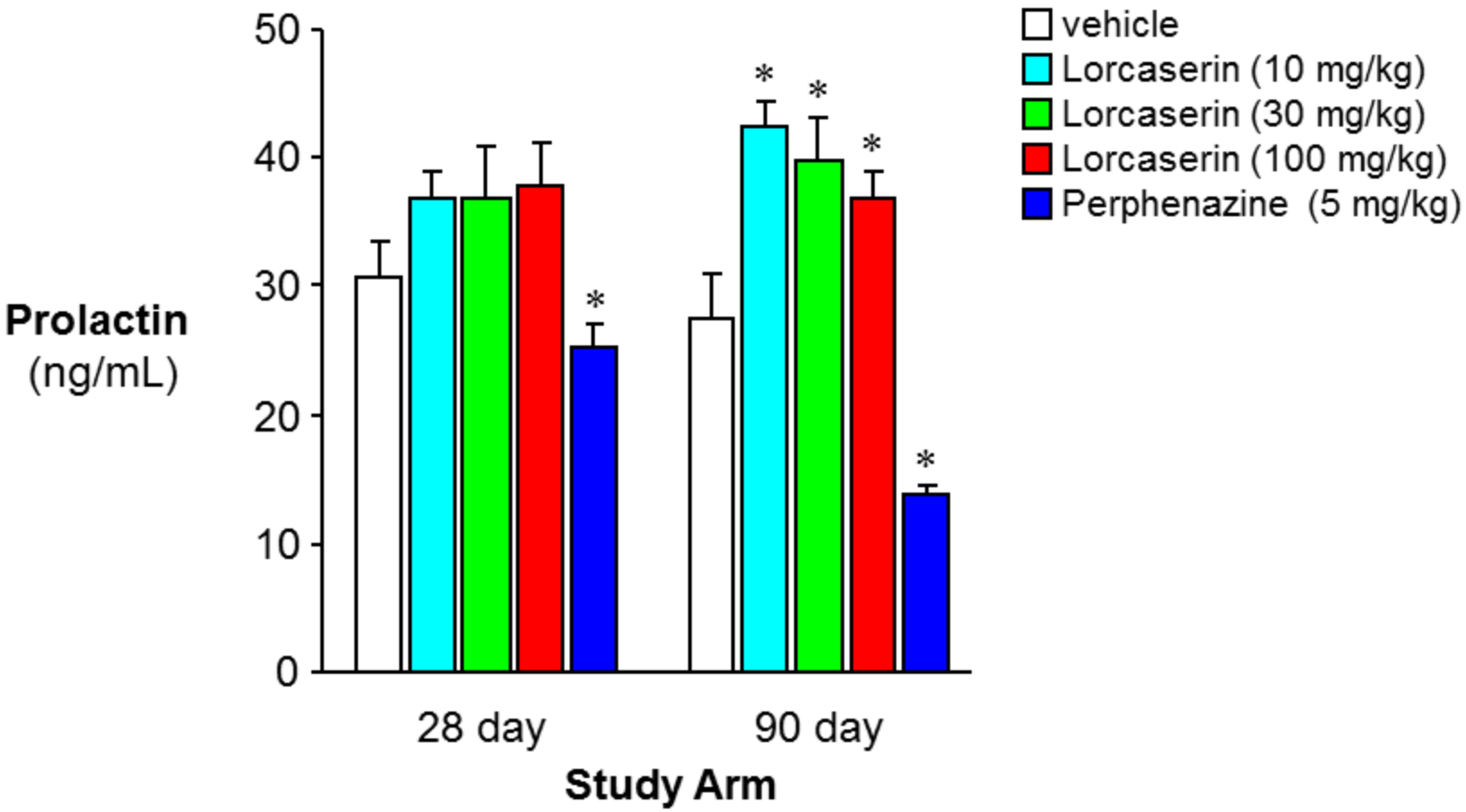


Mean plasma prolactin



All n = 56-60 per group; *p < 0.01 vs. vehicle

Lorcaserin Increases Pituitary Prolactin



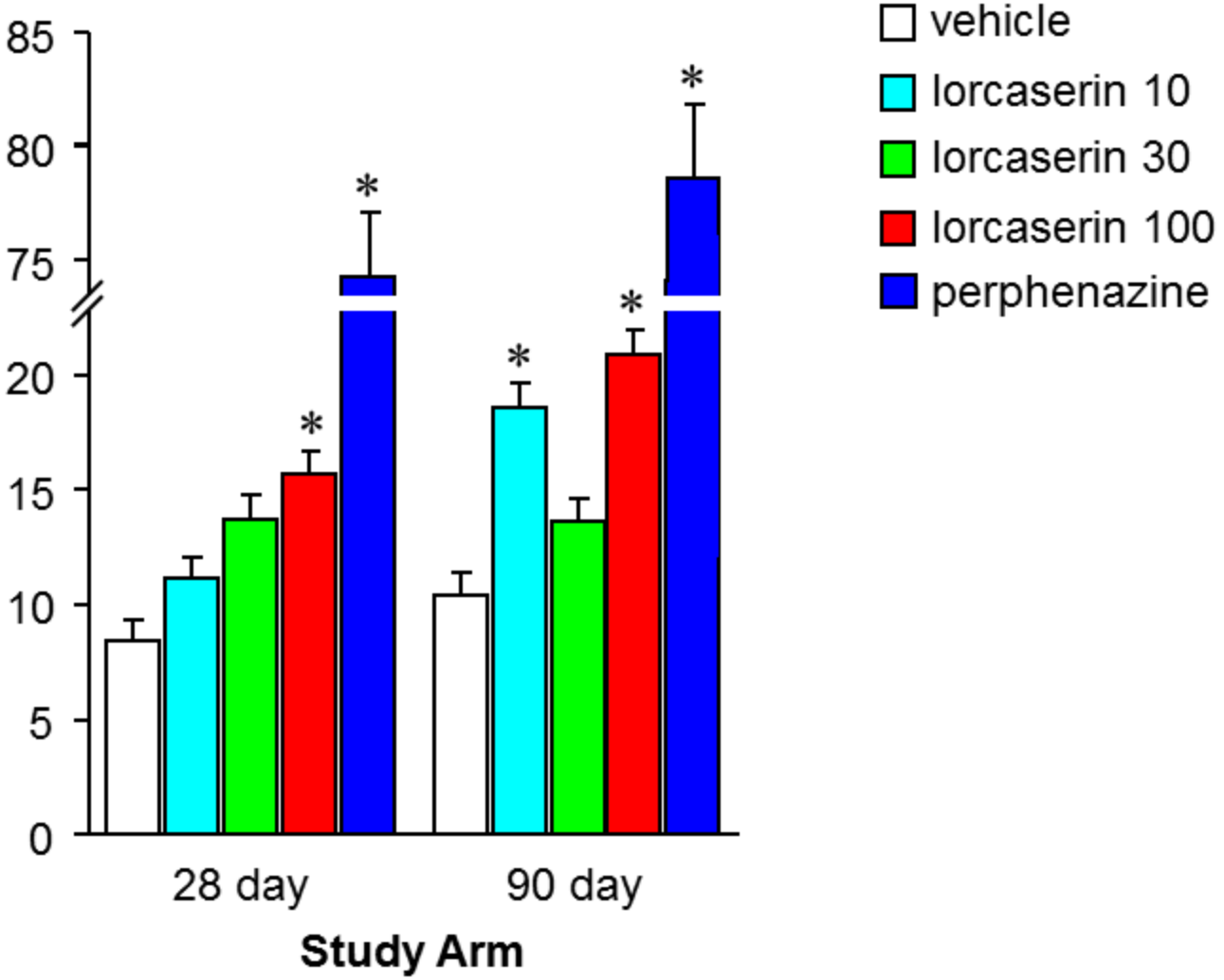
All n = 56-60 per group
* p < 0.05 vs. vehicle

Mammary Tissue Analysis

- Mammary glands harvested at days 28 and 90 of study
- Tissue sent to independent labs for blinded analysis
- Analyses included:
  - Histomorphology (H&E, Whole-mount)
  - Tissue proliferation marker proliferating cell nuclear antigen (PCNA)

Lorcaserin Treatment Induces Changes Characteristic of Hormonal Stimulation

Mammary Gland Hyperplasia
(% Lobular Structures)



All n = 56-60 per group
* p < 0.01 vs. sham vehicle

Prolactin Mechanistic Studies

Hypophysectomy

Group	Treatment	Surgery	Hyperplasia Score	
			Mean	SEM
1	Vehicle	Sham	0.71	0.15
2	Vehicle	Hypophysectomy	0.34	0.09
3	Lorcaserin	Sham	1.59	0.14**
4	Lorcaserin	Hypophysectomy	0.62	0.11

Prolactin Receptor Blockade

Group	Treatment	Co-treatment	Proliferation (PCNA)	
			Mean	SEM
1	Vehicle	Vehicle	1.64	0.38
2	Vehicle	S179D	1.93	0.49
3	Perphenazine	Vehicle	6.05	0.71
4	Perphenazine	S179D	4.57	0.52
5	Lorcaserin	Vehicle	3.79	0.61*
6	Lorcaserin	S179D	2.14	0.38#

** $p < 0.01$ versus all other groups

* $p < 0.05$ vs. vehicle-vehicle; #$p < 0.05$ vs. lorcaserin-vehicle

Results of Rat Mechanistic Studies

1. **Does lorcaserin increase prolactin?**
   - Plasma and pituitary prolactin elevated by lorcaserin

2. **Does treatment with lorcaserin cause measurable changes in mammary tissue?**
   - Morphological changes in mammary tissue after lorcaserin dosing consistent with prolactin stimulation

3. **Can prolactin be linked to tissue changes?**
   - Pituitary removal and prolactin receptor antagonist treatment prevented lorcaserin-induced mammary tissue changes

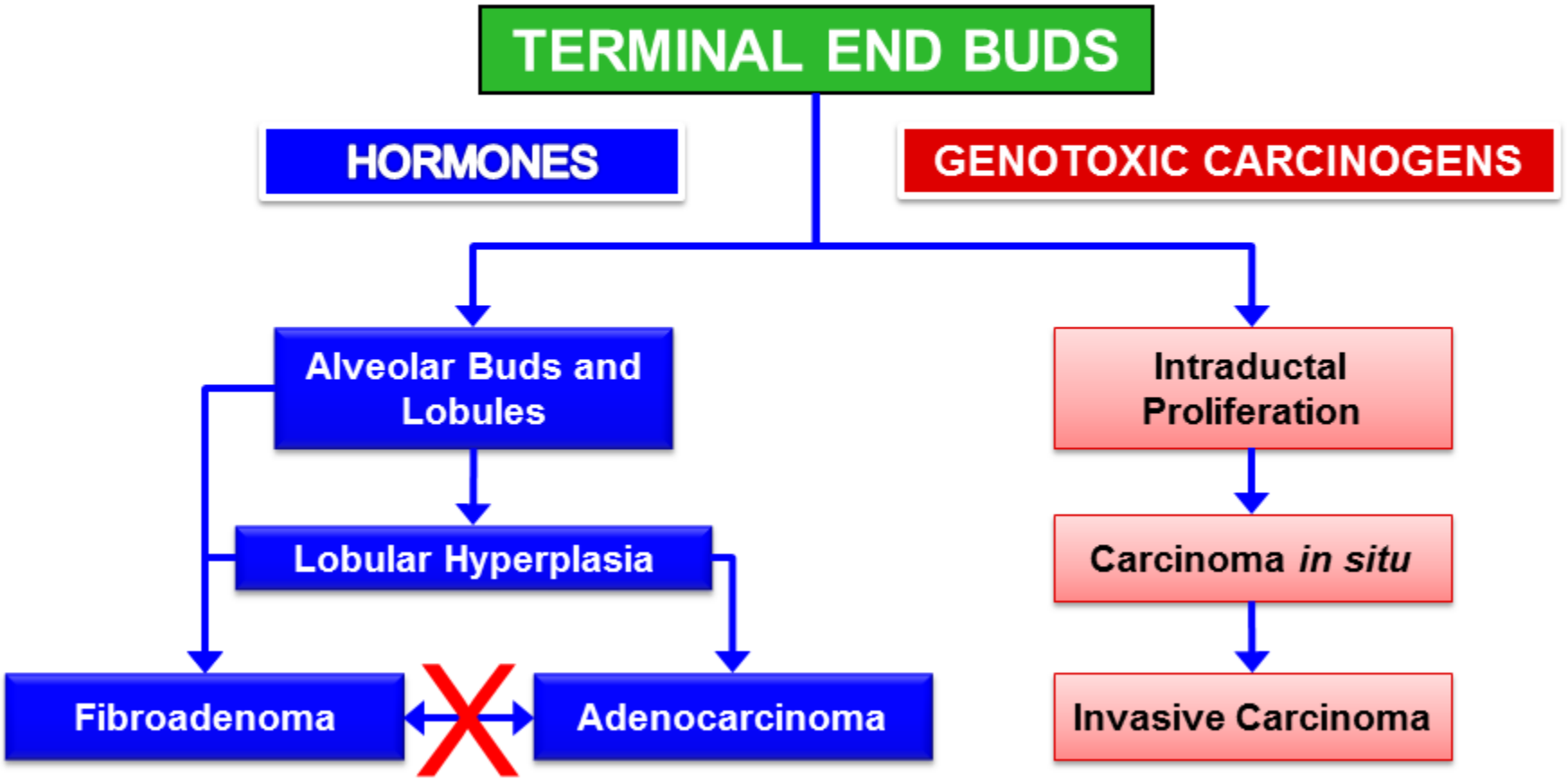
Preclinical Summary: Margin or Mechanism Have Been Established

	Margin or Mechanism
Mammary gland adenocarcinoma	Margin ≥ 24
Mammary gland fibroadenoma	Mechanism
Brain astrocytoma	Margin ≥ 70

Review of Rat Mammary Gland Pathogenesis: Relevance to Human Risk

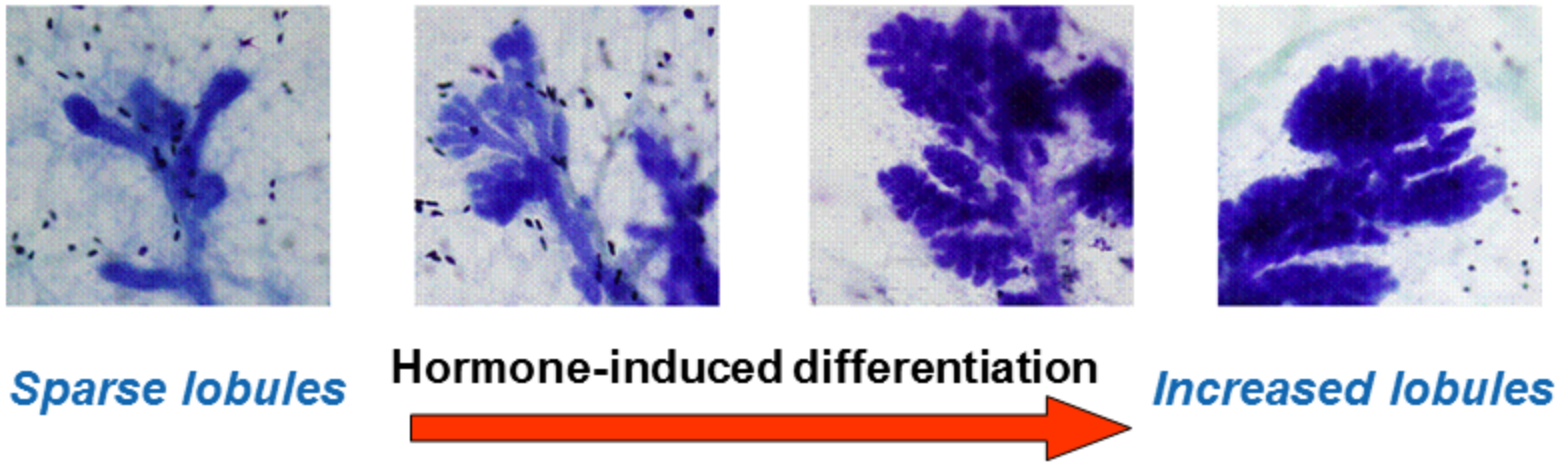
Samuel Cohen, MD, PhD, DABP
Professor of Pathology/Microbiology and
Endowed Professor of Oncology, UNMC
Fellow, Academy of Toxicological Sciences

Rat Mammary Tumor Development



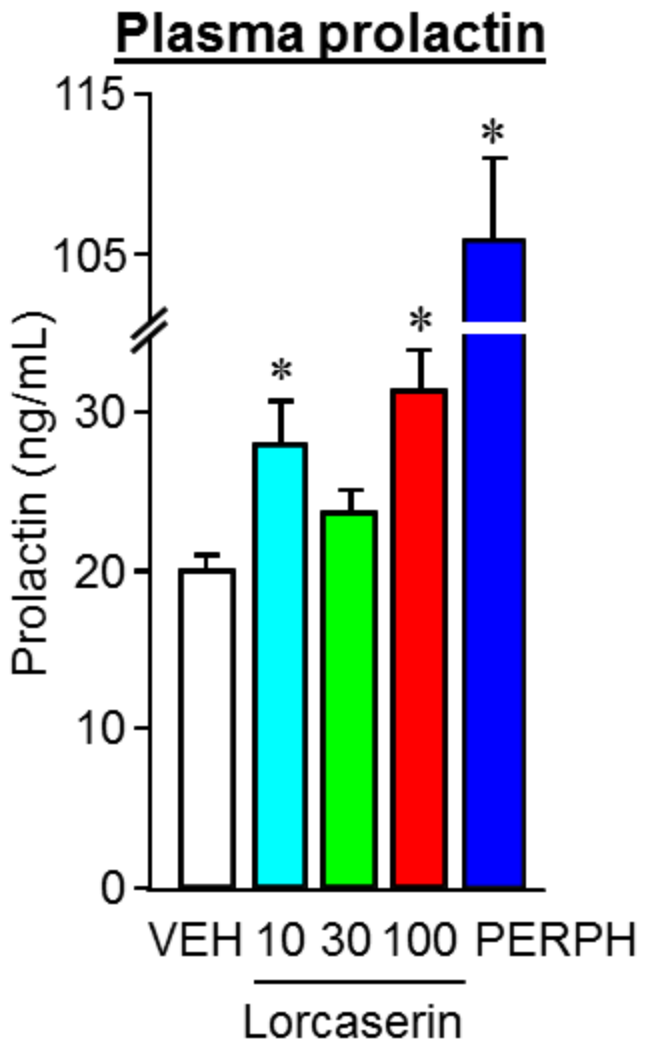
Modified from Russo and Russo 1996

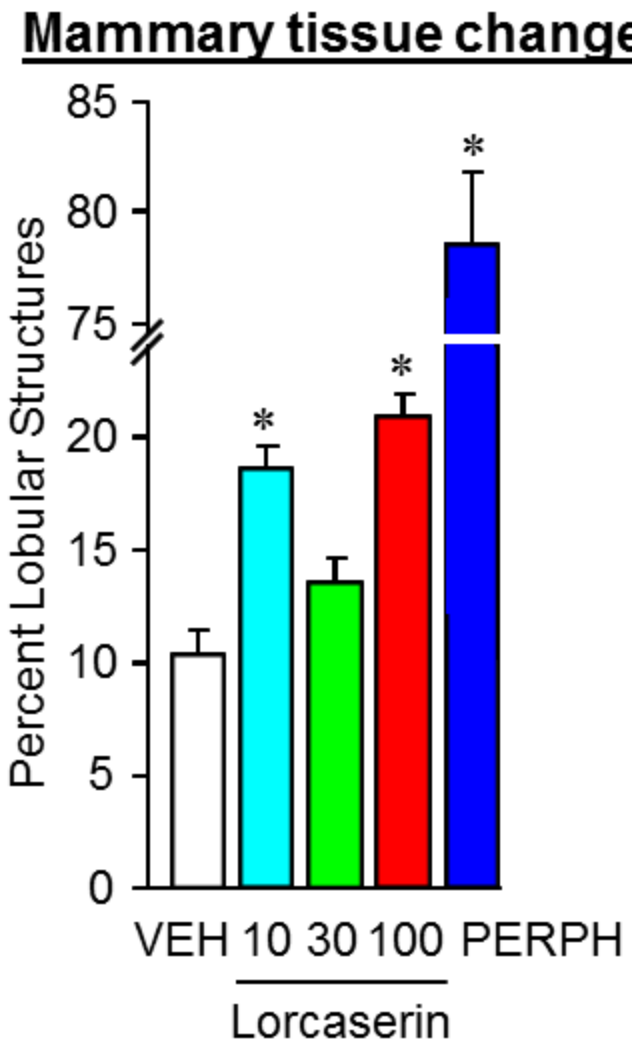
Rat Mammary Gland Changes Characteristic of Hormonal Stimulation (Whole Mount Technique)



Adapted from Russo and Russo (1996) *Environ Health Perspect 104:* 938

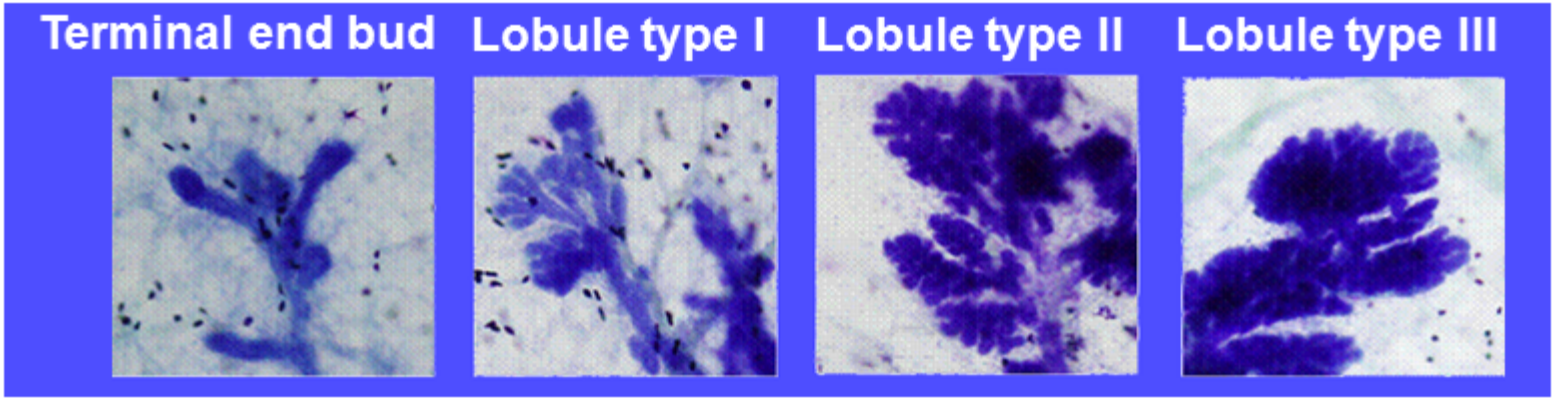
Lorcaserin Mediated Plasma Prolactin and Mammary Tissue Changes





* p < 0.01 vs. sham vehicle

Prolactin Effects on Mammary Gland Structure



Cell Proliferation/Differentiation

Rat	+	+	+	+
Human	–	–	–	+

Tumor Development

Rat	+	+	+	–
Human	–	–	–	–

Adapted from Russo and Russo (1996) *Environ Health Perspect 104:* 938

Role of Prolactin in Mammary Gland in Rat and Human

- Rat:
  - Prolactin induces proliferation and differentiation of susceptible cell populations
  - Prolactin strongly influences development of lobular structures into fibroadenomas
- Human:
  - Prolactin primarily affects lactation
  - Prolactin does not have proliferative or differentiation effects on susceptible cell populations at low levels
  - Prolactin does not cause fibroadenomas

Conclusions

- Lorcaserin effects on the mammary gland are prolactin mediated
- Rat fibroadenomas are not relevant to human risk
- Risk of lorcaserin-induced mammary tumors in humans is negligible

Arena

Conclusion

Dominic Behan, PhD
Exec. Vice President & Chief Scientific Officer
Arena Pharmaceuticals

Body of Evidence Supports Favorable Benefit-Risk Profile of Lorcaserin

- Clinically meaningful weight loss: improvements in biomarkers of cardiovascular and metabolic risk
- Clinically meaningful improvements in HbA1c and fasting plasma glucose in patients with type 2 diabetes
- Consistent safety profile/no clinically significant safety signals
- Preclinical findings: either substantial margins and/or rat specific mechanism

Backup Slides

Cardiovascular 5-HT_{2B} Expression

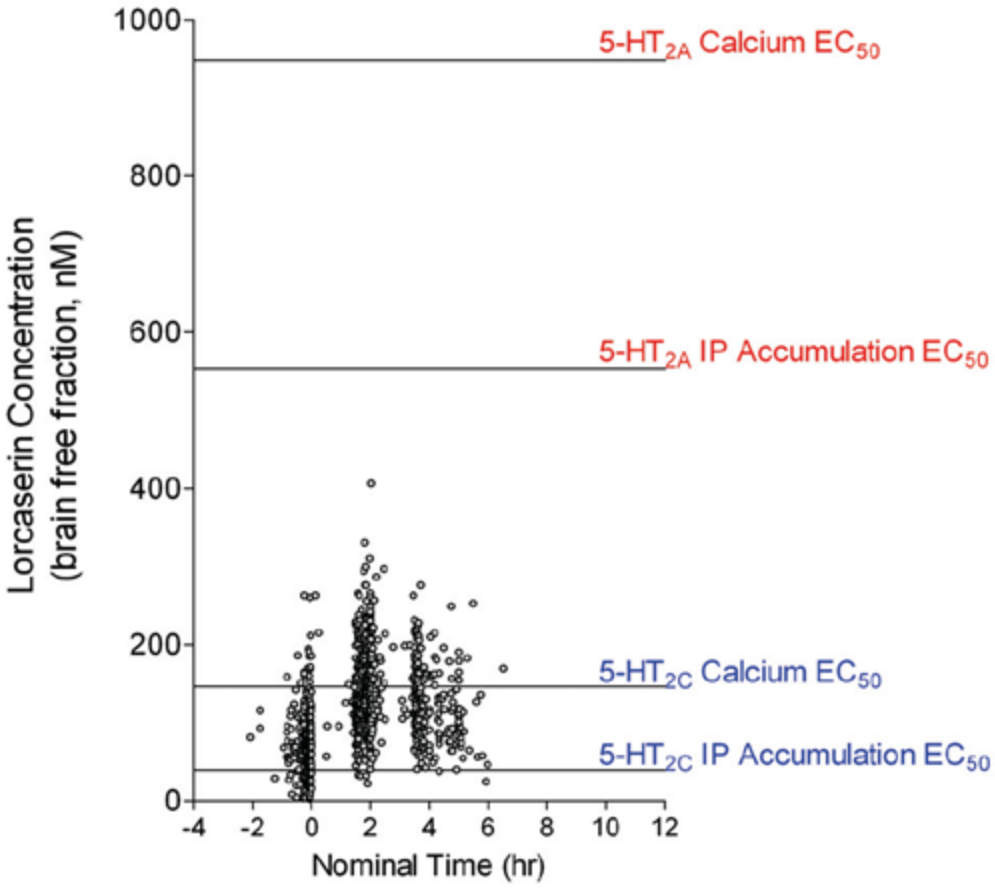
5-HT_{2B} expression levels in cardiovascular tissue

Species	Tissue	B_{max} (fmol/mg)	Reference
Mouse	Cardiomyocyte	110	[1]
Mouse	Cardiac fibroblast	45	[1]
Mouse	Lung vascular bed explants	25	[2]
Human	Left ventricle biopsy (CHF)	114	[1]
Human	Left ventricle biopsy (normal)	~25	[1]

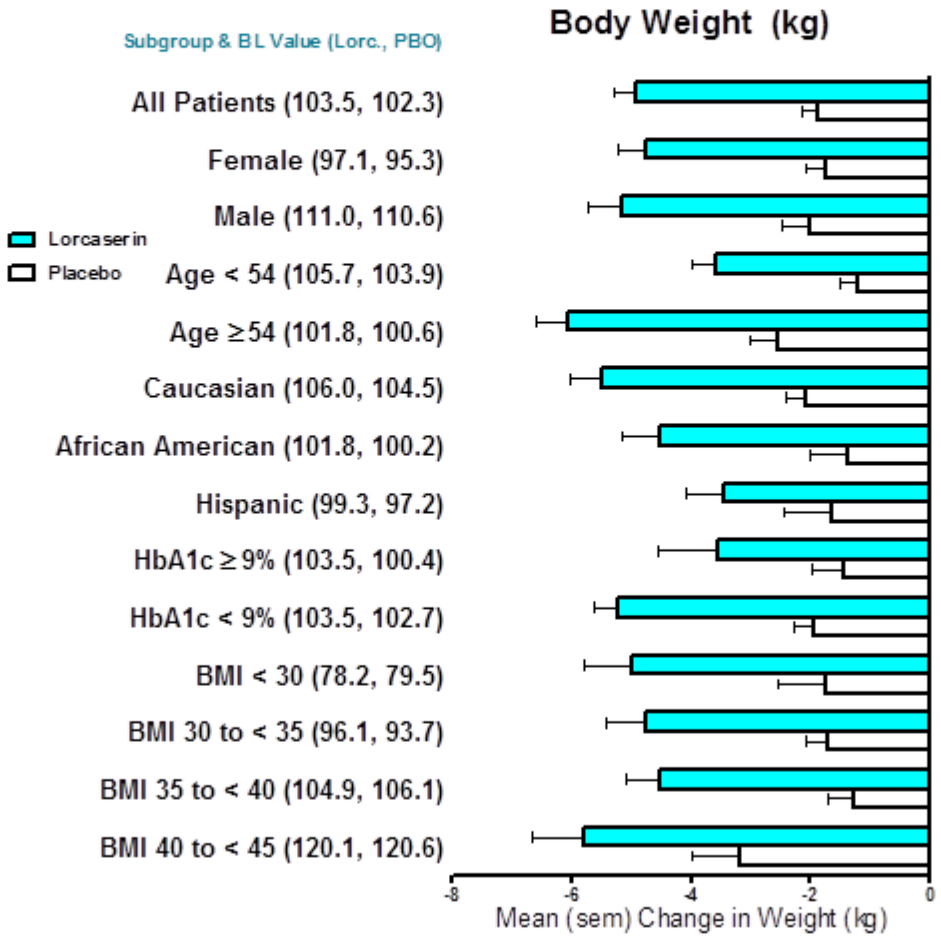
[1] Circ. Res. (2009) 104:113-23. [2] Nature Medicine (2002) 8:1129-35

Receptor reserve effects not observed in cells expressing up to 300 fmol/mg

Extrapolated Lorcaserin Exposure in Human Brain



Change in Body Weight by Demographic Subgroup – Study 010



Change in Heart Rate, Systolic BP, and Diastolic BP by Responder Status (≥ 5% at Week 52, MITT/LOCF) in Study 010

CFB Mean (SEM)	Responders		Non-Responders	
	Placebo N=40	10 mg BID N=94	Placebo N=208	10 mg BID N=157
Heart rate, bpm	-1.60 (1.48)	-3.37 (1.05)	-0.01 (0.62)	-0.75 (0.69)
Diastolic BP, mmHg	-1.30 (1.77)	-1.59 (0.93)	-1.16 (0.57)	-0.79 (0.76)
Systolic BP, mmHg	0.60 (2.66)	-2.54 (1.58)	-1.19 (0.91)	0.20 (1.00)

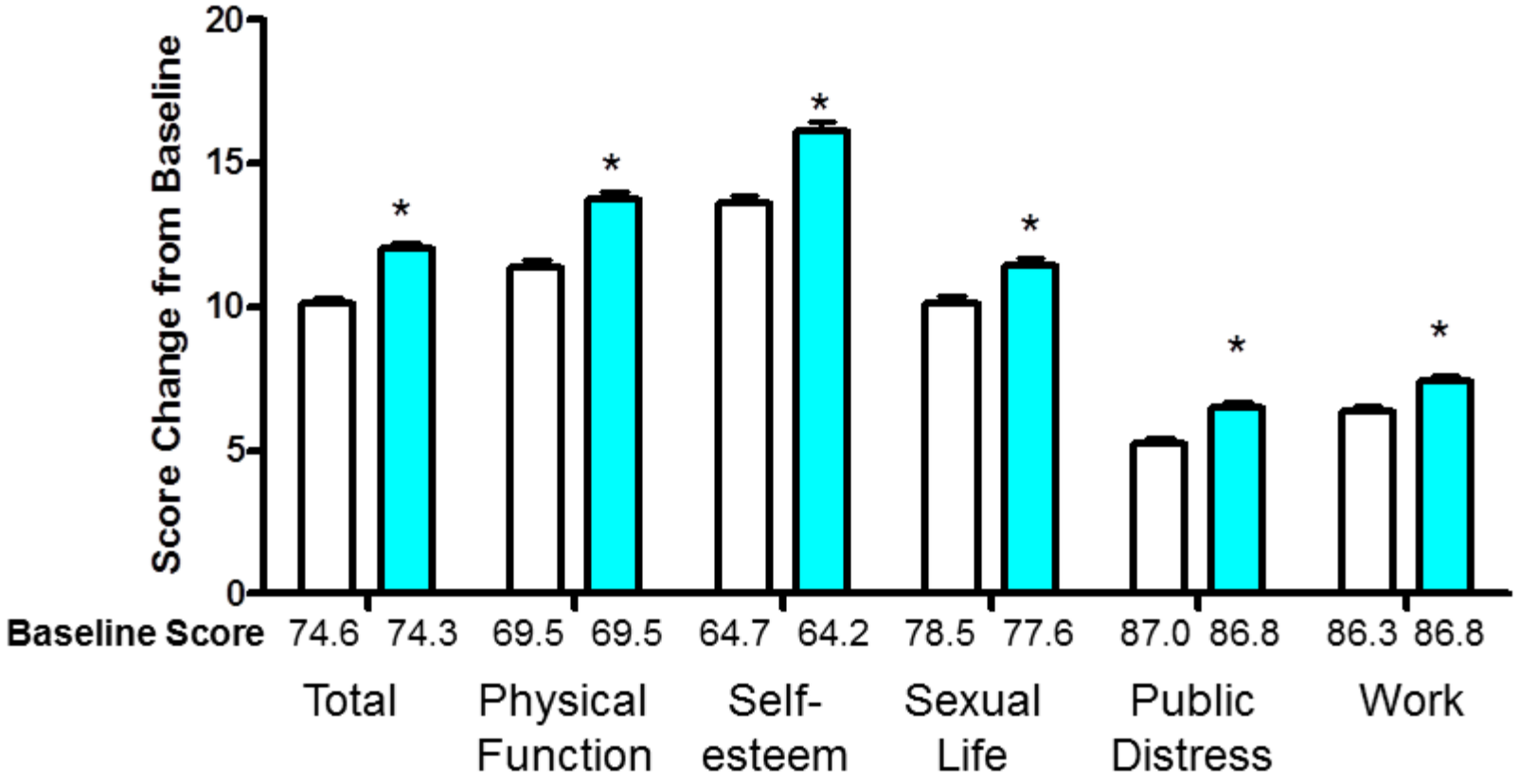
Based on MITT population and LOCF
CFB = change from baseline

Change in Heart Rate, Systolic BP, and Diastolic BP by Responder Status (≥ 5% at Week 52, MITT/LOCF) in Studies 009 and 011

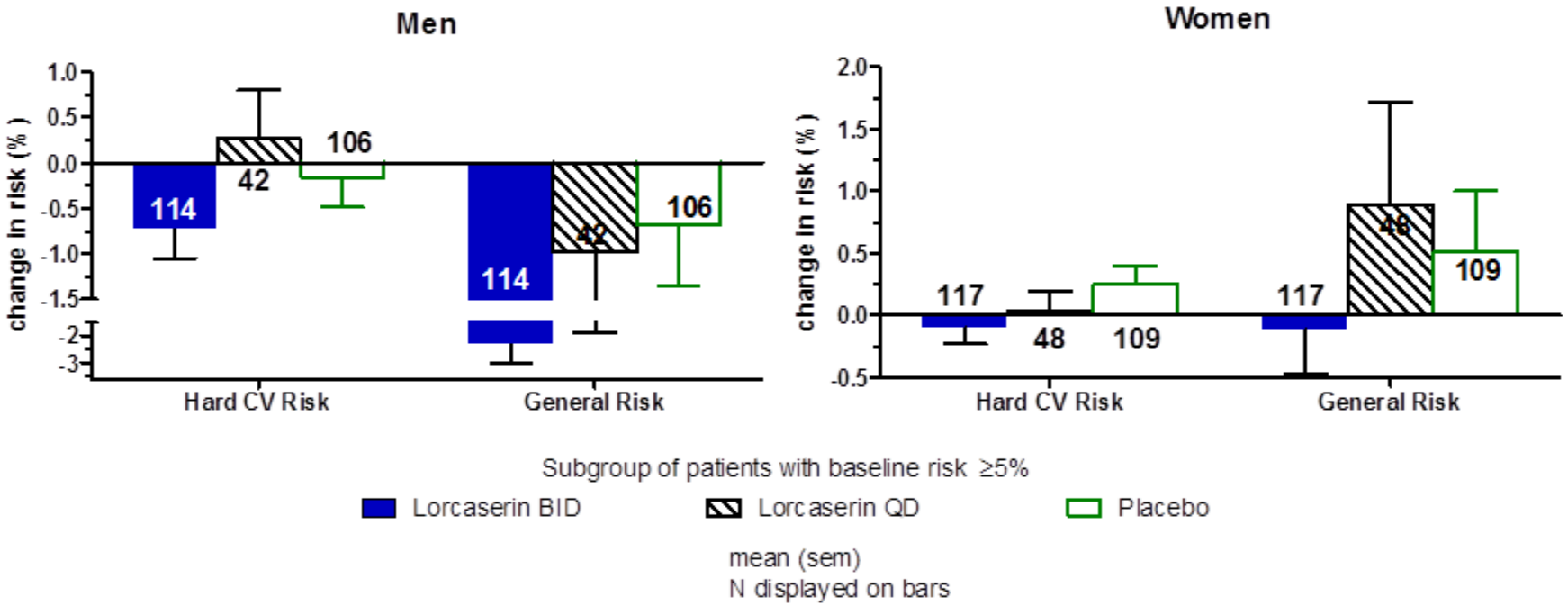
	Responders		Non-Responders	
CFB Mean (SEM)	Placebo N=687	10 mg BID N=1460	Placebo N=2351	10 mg BID N=1636
Heart rate, bpm	-2.68 (0.36)	-2.25 (0.24)	0.23 (0.19)	-0.24 (0.22)
Diastolic BP, mmHg	-2.97 (0.33)	-2.68 (0.23)	-0.47 (0.18)	-0.44 (0.22)
Systolic BP, mmHg	-3.84 (0.44)	-3.33 (0.32)	-0.23 (0.24)	-0.30 (0.30)

Based on MITT population and LOCF
CFB = change from baseline

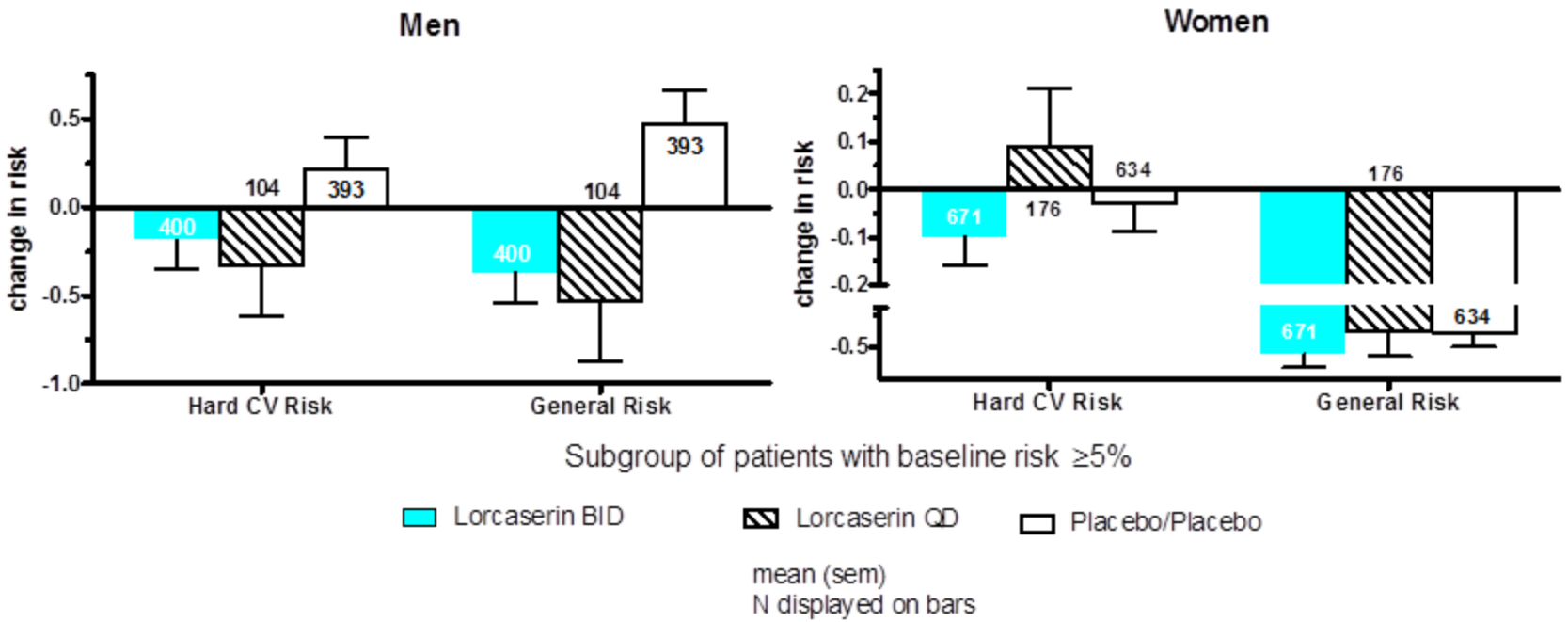
Changes from Baseline in Quality of Life Scores: Studies 009 and 011, MITT-LOCF



Correction: Figure 20 Dose Effect on Framingham Risk Scores in Study APD356-010: MITT/LOCF



Framingham Risk Score Change from Baseline at Week 52 Pooled Studies 009 and 011: MITT Population



Patients with FDA-Defined Valvulopathy at Baseline in Pooled Phase 3 Studies

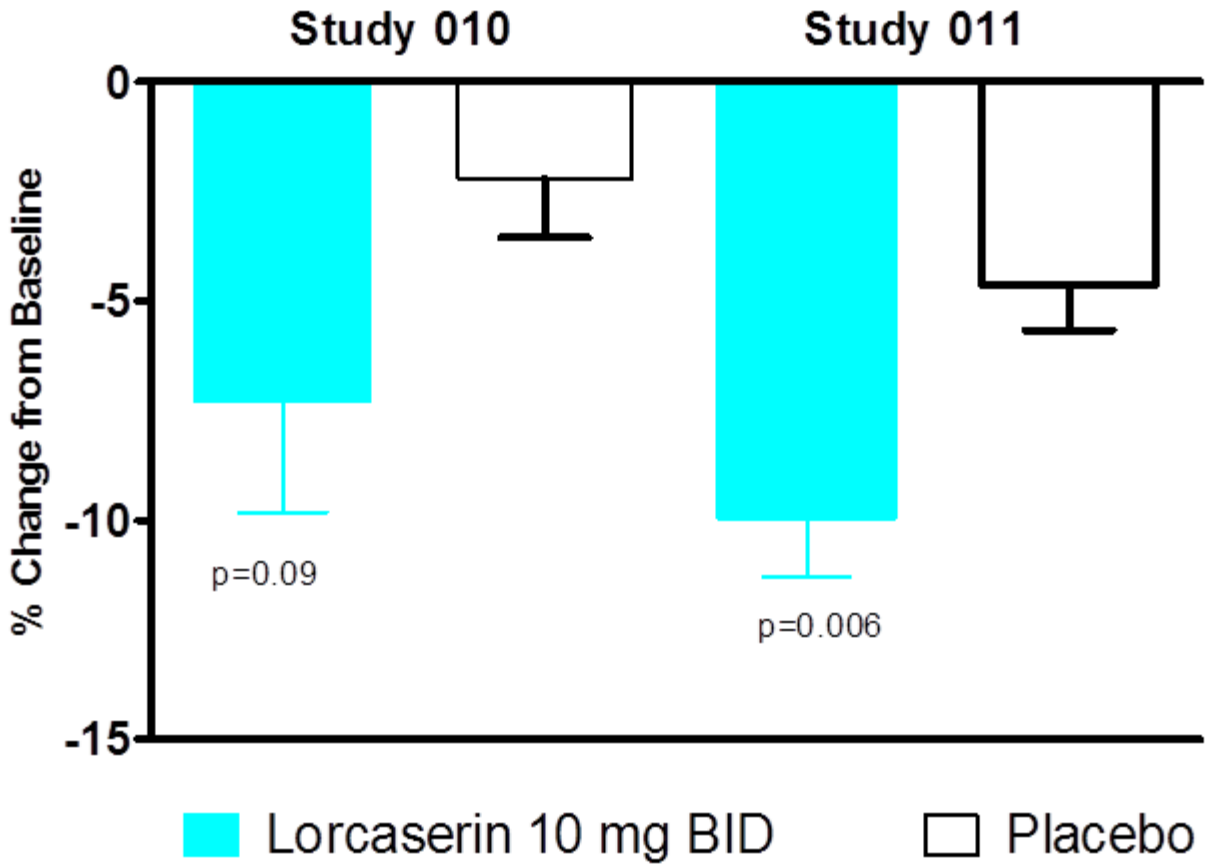
Baseline	Placebo N=60	Lorcaserin 10 mg BID N=75
Valvulopathy still present at Week 24	61.4%	70.3%
Valvulopathy still present at Week 52	60.0%	62.7%

Note: Safety population with last non-missing post baseline observation carried forward.

FDA-Defined VHD by Subgroup, Phase 3 Trials Pooled, 5% Weight-Loss Responder Status (Table 60 FDA Briefing Book)

	Lorcaserin 10 mg BID	Placebo	Relative Risk (95% CI)
Responders	35/1288 (2.7)	18/392 (3.0)	0.86 (0.49, 1.50)
Non-Responders	22/1003 (2.2)	29/1516 (1.9)	1.15 (0.66, 1.99)

Total Body Fat % Change from Baseline to Week 52 Studies 010 and 011: MITT Population



DEXA performed in the Studies 010 and 011 only.
Study 010 sample size: 23 in Placebo and 18 in Lorcaserin
Study 011 sample size: 69 in Placebo and 85 in Lorcaserin

Roth Study – Key Results

5-HT_{2B} Receptor EC_{50} Values for 4 Signaling Pathways

	Calcium	IP Accumulation	β-Arrestin	pERK
Compounds Associated with Valvulopathy				
Serotonin	1.8	9.3	0.26	2.7
Pergolide	63*	6.3	0.91	63*
Cabergoline	209*	0.76	3.0	110*
Nordexfenfluramine	18	26	1.9	158
Methylergonovine	NR	0.06	0.87	79*
Drugs with Lower 5-HT_{2B} Activity Identified by the Roth et al. and Not Associated with Valvulopathy				
Fenoldopam	331	204	129	331
Guanfacine	776	6310	759	1070
Oxymetazoline	331	676	141	933
Quinidine	794	1200	166	1550
Ropinirole	NR	14400	2820	14100
Xylometazoline	1320	4070	427	3500
Lorcaserin	1040	2380	119	1820

All EC_{50} values are in nM

NR – No Response. * Potency likely underestimated in this assay due to slow receptor-association kinetics

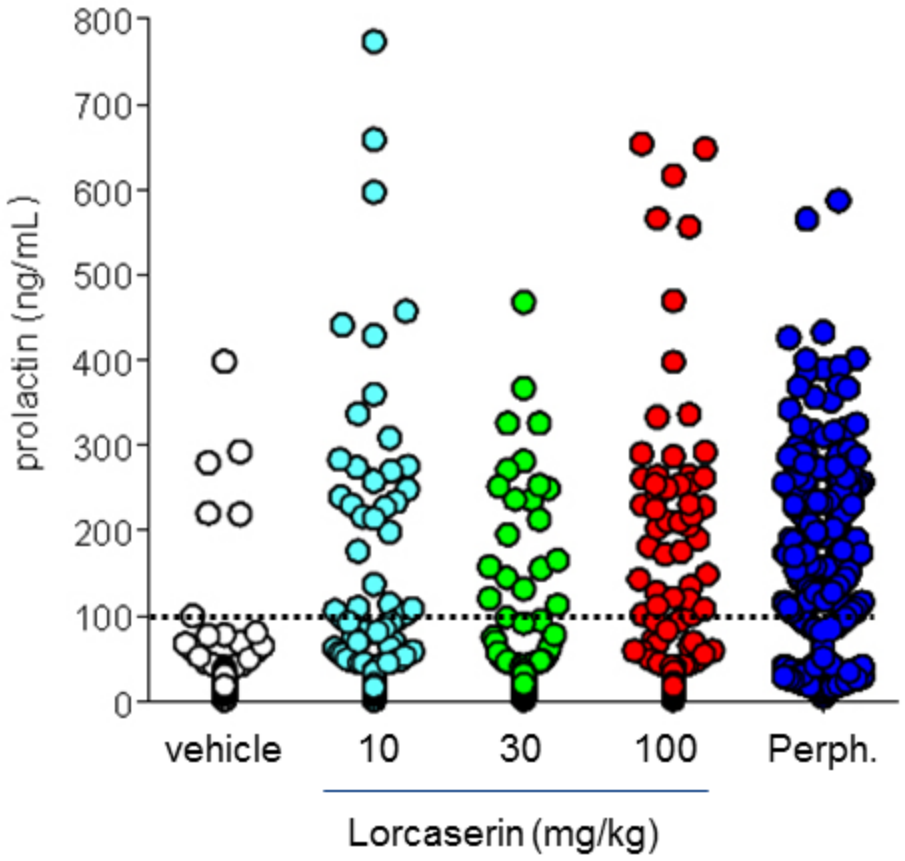
Typical doses of norfenfluramine & pergolide were sufficient to drive 5-HT_{2B} signaling

Drug	EC_{50} 5-HT_{2B} (nM)[a]	Plasma free fraction (nM)	Valvulopathy Incidence, (RR)
Pergolide	6	100	7.1[b]
(+)Norfenfluramine	26	44	2.2[c] 2.32[d]

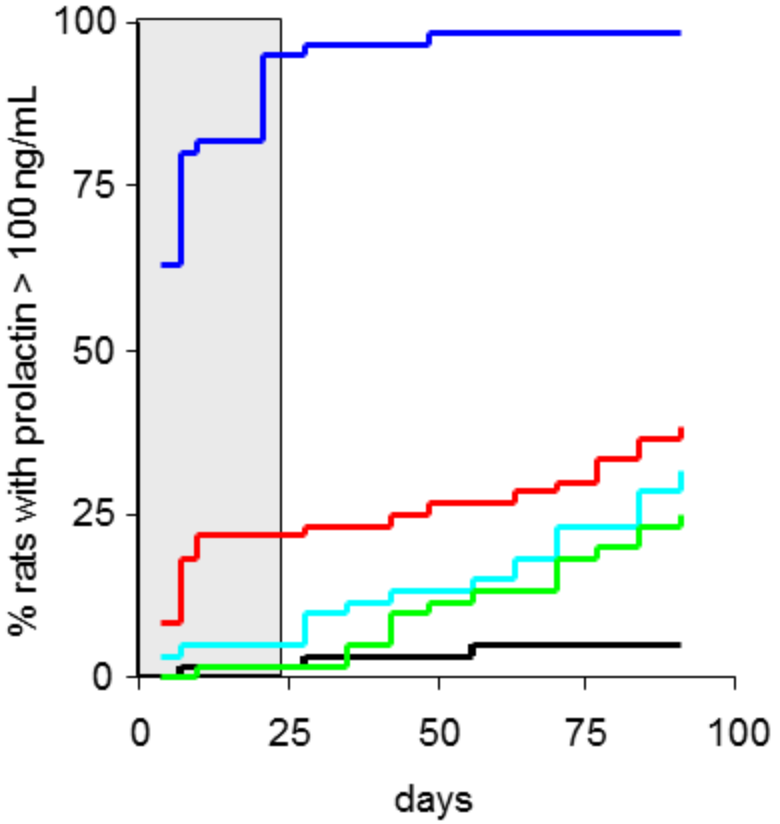
[a] IP accumulation data; [b] Schade et al. NEJM 2007; c Sachdev, et al. Am. Heart J. 2002;
[d] Loke et al. BMC Clin. Pharmacol 2002.

Lorcaserin Increases Plasma Prolactin During a Three-month Study

Single point weekly prolactin reads



Time to first event



Proportion of Patients who Developed FDA-Defined Valvulopathy by Week 52% Weight Loss Tertiles (Pooled Phase 3 Studies)

n (%)	Placebo	Lorcaserin 10 mg BID	RR (95% CI)[a]
≤T1	18 (2.84)	39 (2.85)	0.97 (0.56, 1.69)
T1<-≤T2	15 (1.77)	15 (1.93)	1.11 (0.54, 2.26)
>T2	19 (1.80)	10 (1.85)	1.04 (0.49, 2.20)

T1 = -5.41, T2 = -0.93

Ischaemic HD and Cerebrovascular Event SMQs in All Phase III Studies

Group n/N (%)	PBO	BID
All Pts	20/3437 (0.6)	23/3451 (0.7)
Responder	7/729 (1.0)	7/1552 (0.5)
Non-Responder	13/2711 (0.5)	16/1899 (0.8)

Note: Responders by W52 weight loss >/= 5%.

hsCRP and Fibrinogen Changes from Baseline to Week 52 in the Study 009: Post-Hoc Analysis using MITT Population

Mean ± SE	Baseline	Week 52	Change from Baseline	p-Value
CRP (mg/L)				
Placebo	5.36 ± 0.20	5.21 ± 0.17	-0.17 ± 0.19	
Lorcaserin 10 mg BID	5.51 ± 0.19	4.32 ± 0.15	-1.19 ± 0.18	< 0.0001
Fibrinogen (mg/dL)				
Placebo	363.2 ± 2.3	353.0 ± 2.4	-10.6 ± 2.1	
Lorcaserin 10 mg BID	364.8 ± 2.2	343.1 ± 2.2	-21.5 ± 2.2	0.0002

hsCRP Change from Baseline to Week 52 in the Study 010: MITT Population

Mean ± SE (mg/L)	Baseline	Week 52	Change from Baseline	p-Value
Placebo	5.44 ± 6.66	4.83 ± 6.55	-0.61 ± 0.34	
Lorcaserin 10 mg BID	6.64 ± 9.57	4.79 ± 5.80	-1.85 ± 0.48	0.1500[a]

a p-Value is for difference from placebo in LS mean change from baseline

Change in Lipid Parameters by Responder Status at Week 52 in Studies 009 and 011

CFB Mean (SEM)	Responders		Non-Responders	
	Placebo N=682	10 mg BID N=1444	Placebo N=2098	10 mg BID N=1438
Triglycerides, mg/dL	-12.9 (1.2)	-14.5 (0.8)	3.4 (0.8)	4.1 (1.2)
Total Cholesterol, mg/dL	-1.1 (0.5)	-2.1 (0.4)	0.8 (0.3)	0.5 (0.3)
LDL, mg/dL	2.0 (0.9)	0.6 (0.6)	3.3 (0.5)	2.7 (0.5)
Baseline HDL, mg/dL	4.3 (0.6)	4.0 (0.4)	-0.7 (0.3)	-0.4 (0.3)

Based on MITT population and LOCF
CFB = change from baseline